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Original Research Article

Evaluation of Immediate Renal and Metabolic Dysfunction in Hypoxic Ischemic Encephalopathy in Neonates

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Abstract: ***Background:*** Hypoxic ischemic encephalopathy (HIE) neonates have both transient and long-lasting effects on the neurologic, pulmonary, cardiac, hepatic, gastrointestinal tract, renal, metabolic, and hematologic as well as coagulation systems. Both the disease process and the treatment option of "therapeutic hypothermia" can cause hemodynamic instability. HIE causes damage to almost every tissue and organ. It has both transient and long-lasting effects on the renal and metabolic system of the neonates. ***Objective:*** To assess Renal and metabolic functions in hypoxic ischemic encephalopathy neonates. ***Methods:*** This cross-sectional type of descriptive study was conducted in the Department of Pediatrics at Rajshahi Medical College Hospital, Rajshahi over a period of 2years from July 2021 to June 2023. Based on predefined eligibility criteria, a total number of 70 neonates with HIE stage II and III were included in this study. Data was collected and analyzed by using the 'Statistical Package for Social Sciences (SPSS) software, 24-version. A chi-square test was used to see the relationship of organ dysfunctions between stage II and stage III hypoxic ischemic encephalopathy neonates. ***Results:*** Out of 70 hypoxic ischemic encephalopathy neonates, 55.70% neonates had stage-II and 44.30% had stage-III hypoxic ischemic encephalopathy. Mean age of the neonates was 10.81±8.08 hours, about 68.60% were male and 31.40% were female. More than half of the patients, 51.40%, had renal and metabolic dysfunctions. **Conclusion:** Ischemic injury to renal and hepatic parenchyma is not uncommon. There was statistically significant relationship of age and renal as well as metabolic dysfunction of neonates with stags of hypoxic ischemic encephalopathy ($p < 0.001$ and $p < 0.01$, respectively).

Keywords: Hypoxic Ischemic Encephalopathy, Renal Function, Metabolic.

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Introduction

Perinatal asphyxia leads to Hypoxic Ischemic Encephalopathy (HIE) is a notable cause of mortality in newborns and causes neurodevelopmental disability in infancy and childhood, especially in low-income and middle-income countries.[1] When hypoxia is the cause of neonatal encephalopathy, a clinical syndrome has been described known as hypoxic ischemic encephalopathy (HIE).[2] The main consequence of perinatal asphyxia is HIE and diagnosis of HIE requires abnormal findings on neurological examination within 48 hours after birth. According to the Sarnat and Sarnat staging, the clinical spectrum of HIE is classified as mild, moderate or severe. Infants can progress from mild to moderate and/or severe encephalopathy over the 72

hours following the hypoxic-ischemic insult. Significant proportions of these infants die or survive with severe long-term morbidity. Most of the neonates having HIE present with neurological symptoms. There may be evidence of other end-organ damage such as coagulopathy, raised liver enzymes, acute renal failure, hypotension, pulmonary hypertension and/or respiratory failure.[3]

Hypoxic-ischemic encephalopathy (HIE) is the major cause of neonatal mortality worldwide particularly due to multi-organ involvement (Two or more organ/system). Although insult to the central nervous system is the most common outcome (70%), multi-organ dysfunction including renal (40%), pulmonary (25%), cardiac (30%) and/or gastrointestinal (30%) compromise is not infrequent (Banu et al. 2016). There is consensus of opinion of representative obstetric and pediatric associations that multiorgan or multisystem dysfunction (MOD) is a constant feature of the neonatal postasphyxia syndrome. The MOD phenomenon is mechanistically related to the diving reflex. Multi-organ dysfunction (MOD) is a natural consequence of this defense mechanism because of the cellular damage inflicted on the non-prioritized organs. It is likely that each neonate with clinically detectable heart or brain dysfunction resulting from intrapartum asphyxia would have activated the diving reflex for long enough to cause dysfunction of one or more non-essential organs, particularly kidney and liver. This is expected especially in neonates who prove to have permanent brain injury.[4] Identification of HIE and accurate classification of severity are important for reliable prediction of clinical outcome and long-term planning. Predictions of long-term outcome in the immediate neonatal period are based on clinical, biochemical, electrophysiological, and imaging findings.[5]

There is one of the most life-threatening effects of hypoxic ischemic encephalopathy is renal system involvement. Serum creatinine and blood urea level are elevated in this condition. Higher serum creatinine levels is a bad prognostic marker and significantly correlated to the Sarnat scoring system of HIE.[6] In clinical practice, abnormal biochemical evidence such as blood glucose level, serum electrolytes specially Na+ and K+ , serum calcium are evident of multi-organ dysfunction over 70% of the cases of acute intrapartum asphyxia leading to neonatal encephalopathy.[7] Immediate renal and metabolic function in hypoxic ischemic encephalopathy in neonates was assessed in this study.

Methodology

This was a cross-sectional type of descriptive study done in the Special Care Newborn Unit (SCANU) and neonatal unit in Department of Pediatrics, Rajshahi Medical College Hospital, Rajshahi, Bangladesh. This study was conducted over a period of 2 years from July 2021 to June 2023. Neonates with hypoxic ischemic encephalopathy (stage-II and stage-III) aged up to 48 hours were included in the study. Full term neonates whose gestational age ranged from 37 to 42 weeks, 0 to 48 hours of age, birth weight ≥ 1800 gm., HIE stage-II and stage-III neonates according to Modified Sarnat and Sarnat staging were included in this study. Neonates with major congenital anomalies or clinical condition (dysmorphism, Meconium aspiration syndrome, TORCH infection, Imperforated anus, inborn error of metabolism), any major illness other than hypoxic ischemic encephalopathy, hospitalization due to birth injury, mother or father of neonate who did not give consent to participate in the study were excluded. The sample size was 70. Purposive sampling technique was employed to include the required number of stage II and stage III hypoxic ischemic encephalopathic neonates. Data was collected by using a semi-structured questionnaire. The questionnaire was designed to record information related to the maternal medical history, obstetric history, intrapartum details, details history of the resuscitation. Findings through physical examinations of the newborn were noted on the questionnaire. The neurological conditions of the infant were examined and recorded soon after arrival at the hospital. The initial and subsequent neurological data included level of consciousness, presence of spontaneous movements and coma, altered muscle tone, the age at onset of seizures (subtle or tonic-clonic), and number and dosage of anticonvulsants received were recorded. Threse information along with a clinical description of the attending team was considered for determination of the degree of encephalopathy which was classified according to the criteria by Modified Sarnat and Sarnat within 48 hours of birth. Data were analyzed by using the 'Statistical Package for Social Sciences (SPSS) software, 24-version. Categorical variables were summarized by using numbers and percentages

while continuous variables were summarized by means and standard deviation (SD). A chi-square and Fisher's Exact test were used to see the relationship of organ dysfunctions between stage II and stage III hypoxic ischemic encephalopathy neonates. A p-value < 0.05 was considered statistically significant for all tests.

Results

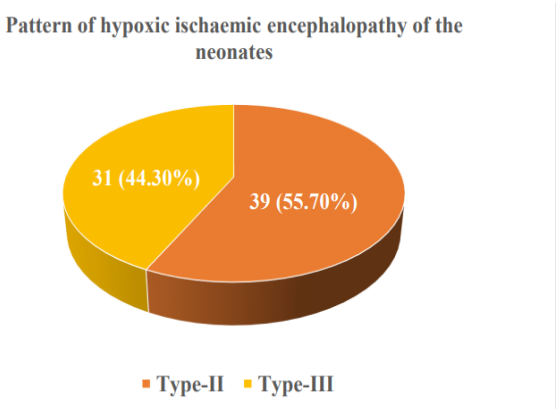

Figure 1: Pattern of Hypoxic Ischemic Encephalopathy of the Neonates (n=70)

More than half (55.70%) of the neonates were type-II and 44.30% were type-III hypoxic ischemic encephalopathy neonates (Figure 1).

Table 1: Distribution of hypoxic ischemic encephalopathy neonates by their Serum Creatinine Level (Renal function) (n=70)

Serum Creatinine Level (Renal function)	Frequency N	Percentage (%)
< 1 mg/dl	34	48.60
≥ 1 mg/dl	36	51.40

Out of 70 hypoxic ischemic encephalopathy neonates, 51.40% had serum creatinine level ≥ 1 mg/dl and 48.60% had serum creatinine level < 1 mg/dl (Table 1).

Table 2: Distribution of Hypoxic Ischemic Encephalopathy Neonates by Their Metabolic Function (n=70)

Metabolic function	Category	Frequency	Percentage (%)
Plasma glucose level	< 40 mg/dl	32	45.70
	≥ 40 mg/d	38	54.390
Serum Sodium	< 135 meq/L	34	48.60
	≥ 135 meq/L	36	51.40
Serum potassium	< 3.5 meq/L	0	00.00
	≥ 3.5 meq/L	70	100
Serum calcium	< 8 meq/L	38	54.30
	≥ 8 meq/L	32	45.70

Table 2 showed the distribution of hypoxic ischemic encephalopathy neonates by their metabolic function. It showed that all the neonates had serum potassium level ≥ 3.5 meq/L, 54.30% neonates had serum calcium level < 8 meq/L and 45.70% had ≥ 8 meq/L, 48.60% neonates had serum sodium level < 135 meq/L and 51.40 had ≥ 135 meq/L, 45.70% neonates had plasma glucose level < 40 mg/dl and 54.30% neonates had ≥ 40 mg/dl.

Table 3: Organ Dysfunctions of Hypoxic Ischemic Encephalopathy Neonates (n=70)

Organ dysfunctions	Category	Frequency	Percentage (%)
Renal dysfunction	Present	36	51.40
	Absent	34	48.60
Metabolic dysfunction	Present	36	51.40
	Absent	34	48.60

A total of 70 neonates, 36(51.40%) had renal and metabolic dysfunction.

Table 4: Relationship Between Stage of Hypoxic Ischemic Encephalopathy and Development of Multi Organ Dysfunction of Neonates (n=70)

Stage of hypoxic ischemic encephalopathy	Multi organ dysfunction		Total Frequency (%)
	Yes Frequency (%)	No Frequency (%)	
Stage II	28 (71.80)	11 (28.20)	39 (55.70)
Stage III	31 (100.00)	0 (0.00)	31 (44.30)
Total	59 (84.30)	11 (15.70)	70 (100.00)

Fisher's Exact Value=8.35, df=1, $p < 0.001$

Table 4 showed the relationship between stages of hypoxic ischemic encephalopathy and development of multi organ dysfunction. Among 39 stage II hypoxic ischemic encephalopathy neonates, 71.80% developed multi organ dysfunction and 28.20% developed single organ dysfunction. On the other hand, among 31 stage III hypoxic ischemic encephalopathy neonates, 100.00% developed multi organ dysfunction.The relationship between stage of hypoxic ischemic encephalopathy and development of multi organ dysfunction was found statistically highly significant ($p < 0.01$)

Table 5: Relationship Between Age of Neonates on Admission and Development of Multi Organ Dysfunction (n=70)

Age of neonates on admission	Multi organ dysfunction		Total Frequency (%)
	Yes Frequency (%)	No Frequency (%)	
< 24 hours	47 (81.00)	11 (19)	58 (82.90)
≥ 24 hours	12 (100)	0 (0.00)	12 (17.10)
Total	59 (84.30)	11 (15.70)	70 (100.00%)

Fisher's Exact Value=1.46, df=1, $p > 0.05$

Table 5 showed the relationship between age of neonates on admission and development of multi organ dysfunction. Among 58 neonates who came into hospital < 24 hours, 81.00% developed multi organ dysfunction and 19% developed single organ dysfunction. On the other hand, among 12 neonates who came in hospital ≥ 24 hours, 100% developed multi organ dysfunction. The relationship between age of the neonate on admission and development of multi organ dysfunction was statistically nonsignificant ($p > 0.05$).

Table 6: Relationship of Renal and Metabolic Dysfunctions Between Stage II and Stage III Hypoxic Ischemic Encephalopathy Neonates (n=70)

Organs involved	Dysfunctions	Stage II HIE	Stage III HIE	p value	Significant level
		Frequency (%)			
Renal dysfunction	Present	12 (30.80)	24 (77.40)	< 0.001	S
	Absent	27 (69.20)	7 (22.60)		
Metabolic dysfunction	Present	18 (46.20)	18 (58.10)	0.32	NS
	Absent	21 (53.80)	18 (58.10)		

Among stage II hypoxic ischemic encephalopathy neonates, 33.30%, 40.00%, 2.60% and 30.80% developed renal and metabolic dysfunctions. On the other hand, among stage III hypoxic ischemic encephalopathy neonates 77.40% developed renal dysfunctions. There was a statistically significant difference between stage II and stage III hypoxic ischemic encephalopathy neonates in terms of renal and metabolic dysfunctions ($p < 0.001$ for renal and $p=0.32$ for metabolic (Table 6).

Discussion

Perinatal hypoxic ischemic encephalopathy insults are frequently accompanied by multiorgan system involvement.[6] Although cerebral injury is the most concerning consequence of hypoxic ischemic encephalopathy is renal system involvement. Serum creatinine and blood urea level are elevated in this condition. Higher serum creatinine levels are a bad prognostic marker and significantly correlated to the Sarnat scoring system of HIE.[1] In this study more than half (55.70%) of the neonates were type-II and 44.30% were type-III hypoxic ischemic encephalopathy neonates. Nearly similar findings were found in a study done by Satriano et al. where 66.7% were stage-II and 33.3% were stage-III hypoxic ischemic encephalopathy neonates.[8] But our findings were not similar with a study done by Walas *et al.*, where out of 56.8% of babies with HIE, 27.58% belonged to HIE grade II.[9]

In this study, there was a statistically significant difference between stage II and stage III hypoxic ischemic encephalopathy neonates in terms of renal and metabolic dysfunction ($p < 0.05$) and 51.40% neonates had renal and metabolic dysfunction. Similar findings were found in a study done by Iribarren *et al.* where renal involvement was 52.1% and 42.6% had metabolic dysfunction.[10] Nearly similar findings were also found with the studies done by Tsaousi *et al.* and Hankins *et al*.[11, 4] But this finding was not similar with a study done by Satriano *et al.* where 12.80% neonates had renal dysfunction. Dissimilar findings were also found in several studies.[8, 12-16]

Satriano *et al.* reported that hypocalcaemia was observed in 46.2% neonates, hypoglycemia in 10.3%, hyponatremia in 35.90%, hypokalemia in 20.51% and hyperkalemia in 2.56% neonates.[8] In another study, Iribarren *et al.* reported that 10.5% neonates were hyperkalemic and 52.1% were hypocalcemic.[10] Hypoglycemia, hypocalcemia and hyponatremia were more pronounced with increasing severity of birth asphyxia. The findings of the present study also agreed with them. In this study, there was a statistically significant difference between stage II and stage III hypoxic ischemic encephalopathy neonates in terms of renal and metabolic dysfunction. But renal and metabolic dysfunction was not significantly different between the two groups. Michniewicz *et al.* reported that stage III hypoxic ischemic encephalopathy neonates had statistically higher renal and metabolic dysfunction as compared to stage II HIE neonates.[15]

Multiorgan dysfunction is a part of birth asphyxia due to redistribution of blood flow to the vital organs. Hypoxic ischemic injury to vital organs like brain, kidney, heart, gut and liver results in organ dysfunction and even failure if not corrected promptly. In this study, neonates in stage II, 71.80% developed multi organ dysfunction and 28.20% developed single organ dysfunction. On the other hand, in stage III hypoxic ischemic encephalopathy neonates, 100% developed multi organ dysfunction. The relationship between stages of hypoxic ischemic encephalopathy and development of multi organ dysfunction was found statistically highly significant. In total 84.30% had multi organ dysfunctions and 15.70% had single organ dysfunction. Similar findings were also found in a study of Pattar *et al.* where multi organ dysfunction was 80.7%.[12] But findings were not similar with the study done by Satriano *et al.*, where single organ system involvement was observed in 28.2% neonates and multi organ system involvement was observed in 71.8% neonates.[8] Dissimilar findings were also found with the studies done by Iribarren *et al*.[10] Table 5 showed the relationship between age of neonates on admission and development of multi organ dysfunction. Neonates who came in hospital < 24 hours, 81% developed multi organ dysfunction and 19% developed single organ dysfunction. On the other hand, neonates who came in hospital ≥ 24 hours, 100% developed multi organ dysfunction. So, the relationship between age of neonate on admission and development of multi organ dysfunction was found to be statistically nonsignificant ($p > 0.05$). So far, I have explored no related scientific literatures mentioned such findings. When compared with stage II HIE

infants, stage III HIE infants show a higher incidence of renal and metabolic dysfunction. Multiple organ dysfunctions were observed more commonly in stage III HIE infants in this study where renal dysfunction is significant and metabolic dysfunction showed nonsignificant (Table 6).

Conclusion

Neonates with HIE are commonly present with perinatal asphyxia and have long-term consequences and multiple organ dysfunctions. Results of the study indicated that renal and metabolic systems were commonly affected though renal dysfunction is significant and metabolic dysfunction is insignificant. There was statistically significant relationship of age on admission and development of multi organ dysfunction of neonates with stage of hypoxic ischemic encephalopathy ($p < 0.001$ and $p < 0.01$, respectively). The spectrum of multiple organ dysfunctions emphasized the need for immediate management of asphyxiated neonates. Early assessment of clinical and biochemical profile would be helpful in managing the condition, reducing severity and improving the outcome of illness.

Authors' contributions: BT, BA, BH, RP: Concept and design, data acquisition and interpretation, SMSH, AKMSA: Drafting and final approval. MBH, LSS, CA, MS: Data acquisition, interpretation, drafting, final approval and agreed to be accountable for all aspects of the work. SY: Co guide, BU: Principal guide.

Ethical Approval: Ethical approval of the study was obtained from the Ethical Review Committee, BSMMU, Dhaka. The ethical issues were informed and addressed for future development of management to the participants' parents. Verbal consent had been given by the parents of the affected children.

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Consent for publication: Had been taken.

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