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Correlation of Renal Function with Severity of Hypoxic Ischemic Encephalopathy (HIE) in Egyptian Full Term Neonates

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Abstract

Background: It is often difficult to predict which newborn with HIE will develop impaired renal function so there is an urgent need for publications about relations of severity of HIE and renal function in these infants.

Aim of study: To evaluate renal function in full term neonates with HIE and its correlation with degree of HIE.

Patients and methods: This case-control study was conducted on 72 full term neonates who divided into group (1) included 36 full term neonates diagnosed as HIE according to World Health Organization (WHO) definition of HIE and group (2) included 36 age- and sex-matched, full term neonates as a control group, Serum creatinine was measured at post natal age, CT scan was done for cases.

Results: Serum creatinine level was elevated in first group in comparison to the control group at day 1 and day 7. It was significantly correlated to the Sarnat scoring system of HIE. The means of serum creatinine were significantly increase with the increase in severity of HIE according to Sarnat and Sarnat staging. There was statistically significant difference among serum creatinine levels regarding CT brain findings with marked elevation in serum creatinine which correlate with severity of HIE by CT brain.

Conclusion: Serum creatinine level correlates with the severity of HIE.

Keywords: Renal function; Hypoxic ischemic encephalopathy

Introduction

Hypoxic ischemic encephalopathy (HIE) is one of the most important causes of neonatal morbidity and mortality worldwide. 25% of neonates with HIE develop severe and permanent neurological sequelae including mental retardation, cerebral palsy and epilepsy [1]. Hypoxic ischemic insult triggers a cascade of adverse events that leads to irreversible neuronal and white matter injury over a period of hours to days. Cellular loss occurs in the up new therapeutic modalities for HIE and the increasing knowledge about the pathogenesis of asphyxia-related disorders, it is often difficult to predict which newborn will develop renal perinatal asphyxia lack specificity, implicating the need for predictors for adverse renal outcomes in infants with HIE [2].

Aim of the Work

To evaluate the level of serum creatinine in newborns with HIE and to assess its correlation with degree of HIE severity according to Sarnat and Sarnat scoring and according to brain CT findings.

Subjects and Methods

This prospective case-control study was conducted on 72 neonates who were classified into two groups:

Group (1) included 36 full term neonates (Their gestational age ranged from 37-42 weeks) who were diagnosed as HIE and admitted to the Neonatal Intensive Care Unit (NICU) of Tanta University hospital (TUH) from April 2017 till April 2018.

Neonates were diagnosed with HIE according to World Health Organization (WHO) definition of HIE if they had demonstrated at least two of the following findings: APGAR score <3 at 1 minute or <6 at 5 minutes, arterial pH <7.2 with base deficit >10 mmol/l, and the presence of post natal clinical complications attributed to birth asphyxia, such as seizures, abnormality in state, hypotension requiring inotropic support, severe apnea and oliguria.

Neonatal AKI was diagnosed according to criteria of Kidney Disease Improving Global Outcome (KDIGO) [3].

Group (2) included 36 age- and sex-matched, apparently healthy neonates who were recruited as a control group.

Exclusion criteria:

-If increased serum creatinine was attributed to causes other than HIE such as hypovolemia, sepsis or localized infection.

-If they were diagnosed with life threatening congenital anomalies, inborn errors of metabolism or preterm births.

This study was done after taking consents from parents of included subjects and approval from Research Ethical Committee of Tanta Faculty of Medicine in accordance with declaration of Helsinki.

All subjects were subjected to the following:

Full history taking: Focusing on gestational age, postnatal age, sex, neurological symptoms such as seizures, perinatal maternal and

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fetal history, mode of delivery, APGAR scoring at 1 and 5 minutes and resuscitation steps.

Thorough clinical examination which included:

- General examinations.
- Vital signs and urine output.
- Anthropometric measurements: Weight
- Systemic examination
- Neurological examination
- Level of consciousness: Alert, lethargy or coma.
- Motor system: Power.
- Muscle tone and reflexes.

HIE staging system

HIE was defined as mild, moderate or severe using the Sarnat and Sarnat staging system [4]. The assessed elements included level of consciousness, muscle tone, tendon and complex reflexes, seizures, autonomic function and electroencephalogram (EEG) description.

Laboratory investigations: which were done for all subjects and included:

- CBC.
- Liver function tests.
- Serum electrolytes (Na, K, Ca).
- Arterial Blood gases (ABG): PH, PO_2, PCO_2 and Base excess.
- Serum creatinine: by routine technique.

Imaging techniques

- CT scan: which were done in all cases.

Collection of blood samples

3 ml of venous blood was taken from all studied groups, samples were centrifuged at 4000 rpm for 10 min; serum samples were separated and stored at -2°C to -80°C until assay.

Statistical Analysis

All data were analyzed using (SPSS version 20.0) software for analysis. According to the type of data, the following tests were used to test differences for significance. Differences between frequencies (qualitative variables) and percentages in groups were compared by Chi-square test. Differences between means (quantitative variables) in two parametric groups by t test, ROC curve for cut off, Kappa

			Group 1 (patients) (n=36)	Group 2 (Controls) (n=36)	Statistica l test	P value
Gestational age (weeks)	Mean ± SD		38.27 ± 0.95	38.05 ± 1.05	0.66	0.5
Gender	Male:	No (%)	26 (72.2)	22 (61.1)	0.5	0.48
	Female:	No (%)	10 (27.8)	14 (38.9)		
Mode of delivery	NVD	No (%)	28 (77.7%)	12 (33.3%)	1.77	0.18
	CS	No (%)	8 (22.2%)	24 (66.7%)		
Birth weight (Kg)		Mean ± SD	3.16 ± 0.47	3.15 ± 0.36	0.12	0.89
APGAR score	at 1 min	Mean ± SD	2.5 ± 0.51	6.3 ± 0.84	16.5	0.001*
	at 5 min	Mean ± SD	5 ± 0.87	8.7 ± 0.64	14.5	0.001*
Maternal risk factors	Maternal preeclampsia	No (%)	10 (27.8%)	8 (22.2%)	1.59	0.02*
	Maternal diabetes mellitus	No (%)	8 (22.2%)	2 (5.6%)	2.09	0.14
	PROM	No (%)	8 (22.2%)	2 (5.6%)	1.12	0.28
	Antepartum hemorrhage	No (%)	10 (27.8%)	2 (5.6%)	5.8	0.016*
Maternal risk factors	Maternal renal failure	No (%)	8 (22.2%)	0 (0%)	2.11	0.14
Sarnat and Sarnat Staging of HIE:	Stage 1	No (%)	16 (44.4%)	-	-	-
	Stage 2	No (%)	12 (33.3%)	-		
	Stage 3	No (%)	8 (22.2%)	-		
Resuscitation steps	Free oxygen flow	No (%)	0 (0 %)	14 (38.9%)	8.69	0.003*
	Assisted ventilation (Ambu bagging only)	No (%)	16 (44.4%)	22 (61.1 %)	1	0.31
	ETT	No (%)	12 (33.3%)	0 (0%)	7.2	0.007
	Chest compression	No (%)	6 (16.7%)	0 (0%)	3.27	0.07
	Medications	No (%)	2 (5.6%)	0 (0%)	1.02	0.31
Impaired conscious level:	Alert	No (%)	22 (61.1%)	36 (100%)	0.3	0.1
	Lethargy	No (%)	8 (22.2%)	0 (0%)	5.09	0.00
	Coma	No (%)	6 (16.7%)	0 (0%)	2.4	0.00
Muscle Tone	Normotonia	No (%)	20 (55.6%)	36 (100%)	1.68	0.9
	Hypotonia	No (%)	12 (33.3%)	0 (0%)	9.8	0.00
	Hypertonia	No (%)	6 (16.1%)	0 (0%)	9.12	0.00
Tendon Reflexes	Normal	No (%)	24 (66.7%)	36 (100%)	0.27	0.7
	Abnormal	No (%)	12 (33.3%)	0 (0%)	9.5	0.00
Convulsions	No convulsions	No (%)	18 (50%)	36 (100%)	0.94	0.56
	Tonic-clonic	No (%)	12 (33.3%)	0 (0%)	17.9	0.001*
	Subtle	No (%)	6 (16.7%)	0 (0%)	10.4	0.001*

*P-value <0.05 significant.

Table 1: Demographic and clinical characteristics of the studied cases and the controls.

agreement to test the agreement. P value was set at <0.05 for significant results and <0.001 for high significant result [5].

Results

Table 1 summarized demographic data of the studied subjects. There was no significant difference between studied groups as regard gestational age and weight. There was also no significant difference between studied groups as regard sex. There was significant difference between studied groups as regard prenatal history of maternal hypertension and ante-partum hemorrhage. There was no significant difference between studied groups as regard mode of delivery. As regard Apgar score at 1 minute and 5 minutes of cases and controls, there was significant decrease in cases than in controls. As regard resuscitation steps among studied groups, the use of free oxygen flow and ETT were significantly increase in cases than in controls. Regarding clinical presentation of the studied neonates, they were classified according to Sarnat and Sarnat stages of HIE into stages I, II and III. Table 2 summarized the laboratory findings of the studied patients and controls including complete blood picture, ABG, serum electrolytes, liver enzymes, blood urea and serum creatinine. Table 3 showed comparison of serum creatinine level in studied patient subgroups according to Sarnat and Sarnat staging. This table showed that means of serum creatinine were significantly increased with the increase in severity of HIE according to Sarnat and Sarnat staging. Table 4 showed relation between serum creatinine and findings of CT brain among studied cases, there was statistically significant difference among serum creatinine levels regarding CT brain findings with marked elevation in serum creatinine which correlate with severity of HIE by CT brain.

Discussion

Perinatal asphyxia is an insult to the fetus due to lack of oxygen (hypoxia) and/or lack of perfusion (ischemia) to various organs. It is associated with tissue lactic acidosis and hypercapnia. The effect of hypoxia and ischemia may not be identical, but they are difficult to separate clinically. Both factors probably contribute to injury [6].

Hypoxic-ischemic injury is the most important consequence of perinatal asphyxia [5].

Reperfusion of previously ischemic tissue may also promote the formation of excess oxygen free-radicals, which may damage cellular lipids, proteins, nucleic acid, and the blood brain barrier [7].

In response to acute hypoxia, the fetal neonatal cardiovascular system attempts to preserve blood flow to the brain, heart, kidney and adrenals. Multiple organs injury including acute kidney injury (AKI) occurs in 70% of HIE infants, and these must be some evidence of end-organ involvement to meet the definition of birth asphyxia [8].

Previously, it was unknown that the extent of systemic organ involvement might or might not correlate with the severity of encephalopathy. This can be transient and reversible. In fact, the CNS is often the main organ system that has residual sequelae at long term follow-up [9].

Many physiopathological mechanisms involved in the brain damage related to HIE of the newborn. Early assessment of the severity of an acute cerebral lesion secondary to hypoxia-ischemia may provide a very useful basis for preventive or therapeutic.

In our study, regarding brain CT scan, 24 (66.7%) were normal, 4 (11.1%) had brain odema and 8 (22.2%) had sever ischemia.

Our study agreed with the observation made by Volpe that infants with normal CT scans rarely exhibit major neurological deficits on follow-up and infants with scans demonstrating marked diffuse hypodensity are rarely normal on follow-up [10].

Our study disagreed with findings of Tippin et al. [11]. Although CT scan may occasionally show early changes, it is most often normal hours after the insult and may remain unremarkable at later stages, even in patients with extensive neurological damage [12].

In our study, there was significant increase regarding blood urea and serum creatinine levels, in cases group when compared to control group ($p<0.05$). This results were in agreement with Huang et al. [13] who found that serum urea and creatinine level is significantly elevated in their HIE patient group in comparison to control group. Bhantnagar et al. reported also that the concentration of blood urea and creatinine were significantly higher in their hypoxic ischemic patients when compared to control group [14]. These findings were in accordance also with those of Gupta et al. who found that serum creatinine and blood urea were significantly higher in asphyxiated newborns compared to

			Group 1 (patients) (n=36)	Group 2 (Controls) (n=36)	Statistical test	P value
	WBCs	Mean ± SD	14.7 ± 9.9	3.4 ± 1.6	5.09	0.001
	RBCs	Mean ± SD	4.1 ± 1.3	5.2 ± 1.9	2.49	0.015
CBC	HB	Mean ± SD	12.7 ± 1.1	16.4 ± 1.5	1.4	0.14
	Platelets	Mean ± SD	193 ± 91.9	186.1 ± 60.5	0.3	0.76
ABG	PH	No (%)	7.03 ± 0.13	7.39 ± 0.03	11.2-	0.000*
	PCO_2 (mmHg)	No (%)	30.5 ± 12.7	39.2 ± 3.06	2.2	0.02
	PO_2 (mmHg)	Mean ± SD	39.5 ± 16.6	37.1 ± 6.5	7.8	0.001*
	HCO_3 (mmol/L)	Mean ± SD	11.1 ± 2.9	22 ± 2.1	12.5	0.001*
	BE (meq/L)	Mean ± SD	-11.1 ± 3.5	0.55 ± 0.23	3.9	0.35
Serum Ca		Mean ± SD	0.99 ± 0.14	1.25 ± 0.07	11.28	0.001*
Serum Na		Mean ± SD	129.6 ± 7.2	134.3 ± 6.3	2.4	0.016*
Serum K		Mean ± SD	4.4 ± 0.75	4.5 ± 0.1	0.54	0.58
SGPT		Mean ± SD	113.5 ± 114.2	21.1 ± 5.2	3.4	0.002*
SGOT		Mean ± SD	110.2 ± 104.09	20.9 ± 5.06	3.6	0.001*
Serum Creatinine (mg/dl)		Mean ± SD	0.87 ± 0.76	0.36 ± 0.21	2.7	0.01*
Blood urea (mg/dl)		Mean ± SD	64.05 ± 22.7	27.16 ± 5.5	3.1	0.004*

*P-value <0.05 significant

Table 2: Laboratory characteristics of the studied cases and the controls.

	Sarnat I	Sarnat II	Sarnat III	P.value
	n=16	n=12	n=8	
Serum creatinine (mg/dl)	0.51 ± 0.19	0.74 ± 0.25	1.3 ± 0.5	0.001

Table 3: Comparison of serum creatinine level in studied patient subgroups according to Sarnat staging.

CT brain	Serum creatinine	t	p-value
	At day 7 (mg/dl)		
	Mean ± SD		
Normal	0.44 ± 0.15		
Brain odema	0.51 ± 0.01	5.01	0.02
Sever ischemia	0.73 ± 0.011		

Table 4: Comparison between serum creatinine in the studied patients according to findings of CT brain.

those of control group [15]. Our results were in accordance with many previously published articles including those of Gapal et al., Alaro et al., Amardiyanto et al. [16-18].

In this study, results of serum creatinine and blood urea were significantly correlated with the degree of hypoxic ischemic encephalopathy according to Sarnat and Sarnat as the level of serum creatinine in patient subgroups differ according to the Sarnat score. Sarnat stage I patients had a mean level of 0.51 ± 0.19 mg/dl. The mean level of serum creatinine for Sarnat II patients was 0.74 ± 0.25 mg/dl, whereas Sarnat III subgroup had a mean serum creatinine level of 1.3 ± 0.5 mg/dl.

These findings mean that urea and creatinine levels showed a highly significant increase with increased severity of Sarnat stages. These results were in accordance with Gupta et al. who were studying renal failure in asphyxiated neonates and stated that blood urea and serum creatinine were significantly higher in asphyxiated neonates when compared to the control group. A rising trend in the concentrations of blood urea and creatinine was also observed as HIE staging of neonates progressed, and the difference was statistically significant.

Andreoli, Gharehbaghi, Peirovifar, El-Gamasy and Nassar reported that HIE was one of the most prevalent risk factors for AKI in newly born infants [19-21].

In our study, there was significantly increase in serum creatinine in cases with abnormal CT findings when compared by those without brain abnormalities by CT brain and there was significantly increase in serum creatinine in cases with severe ischemia when compared by those with brain edema by CT brain.

Our results were in accordance with Park et al. who were studying the correlation between the severity of hypoxic ischemic encephalopathy and the development of acute renal failure in asphyxiated neonates, found that the greater the degree of HIE, the higher was the incidence of acute renal failure (ARF) [22].

Conclusions

Serum creatinine correlates with the severity of HIE as serum creatinine were significantly increased with the increase in severity of HIE according to Sarnat and Sarnat staging.

There was statistically significant difference among serum creatinine levels regarding brain CT findings with marked elevation in serum creatinine that correlate with severity of HIE by CT of brain. So higher serum creatinine levels was a bad prognostic marker for severity of HIE.

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