**Original Article**

**Relation of Serum Creatinine to Sarnat Scoring and Brain Computerized Tomography of Neonates with Hypoxic Ischemic Encephalopathy. A Single-Center Experience**

*Mohamed A. El-Gamasy, Redha Alarabawy*

Departments of Pediatrics and Diagnostic Radiology, Faculty of Medicine, Tanta University, Tanta, Egypt

**ABSTRACT**

**Background:** It is not easy to suspect whether newly born infants diagnosed as hypoxic ischemic encephalopathy (HIE) will develop impairment of renal function, so there is an urge to scientifically research about correlations of severity of HIE, which is represented by Sarnat scoring and brain computerized axial tomography (CAT) and serum creatinine level in these newly born infants.

**Aim:** To evaluate renal function in the form of serum creatinine levels in full-term neonates with HIE and their correlation with severity degree of HIE, which is represented by Sarnat scoring and CAT.

**Subjects and Methods:** This study was a case–control type. It was conducted on 72 full-term neonates who were classified into group 1, which included 36 full-term neonates who were diagnosed as HIE according to the definition of the World Health Organization and group 2, which included 36 full-term neonates who were matched for age and sex and who served as the control group. Serum creatinine levels were measured at days 1 and 7 postnatally. CAT scans were carried out for cases only.

**Results:** Serum creatinine levels were elevated in group 1 when compared to the control group at days 1 and 7 postnatally. They were significantly correlated to the Sarnat scoring system of HIE, meaning that serum creatinine levels gradually increased with the increase in severity of HIE according to Sarnat and Sarnat staging. A statistically significant difference was observed between serum creatinine levels in patients with different findings of brain CAT, meaning that more elevation in serum creatinine levels were reported with more severe cases represented by marked changes in brain CAT.

**Conclusion:** Serum creatinine levels correlate with the severity of HIE of neonates according to Sarnat scoring and brain CAT.

**Keywords:** Brain computerized axial tomography, hypoxic ischemic encephalopathy, Sarnat scoring, serum creatinine

**INTRODUCTION**

Hypoxic ischemic encephalopathy (HIE) was reported as an important cause of neonatal morbidity and mortality worldwide.[1,2] About one-quarter of neonates who were diagnosed as HIE develop permanent neurological deficit including mental retardation, cerebral palsy, hearing or visual impairment, and epilepsy.[3] Over a period of hours to days, hypoxic ischemic insult triggers a cascade of adverse events that lead to irreversible grey and/or white matter injury. It is not easy to suspect whether newborn will develop renal impairment. There is an urgent need for prediction of adverse renal outcomes in neonates with HIE.[4]

**Aim of the work:** To evaluate renal function in the form of serum creatinine levels in full-term neonates

**Address for correspondence:** Dr. Mohamed A. El-Gamasy, Department of Pediatrics, Tanta University Hospital, El Giesh Street, Tanta, Gharbia, Egypt. E-mail: mgamsy@gmail.com

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with HIE and their correlation with severity degree of HIE, which is represented by Sarnat scoring and computerized axial tomography (CAT).

**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 to 42 weeks) who were diagnosed as HIE and admitted to the neonatal intensive care unit of Tanta University Hospital, Egypt, from April 2017 till April 2018.

Neonates were diagnosed with HIE according to the World Health Organization definition of HIE if they had shown at least two of the following findings: Apgar score <3 at 1 min or <6 at 5 min, arterial pH <7.2 with base deficit >10 mmol/L, and the presence of postnatal clinical complications, which attributed to birth asphyxia, such as convulsion, abnormality in mental state, hypotension requiring positive inotropic support, severe apnea, and oliguria.

Neonatal acute kidney injury (AKI) was diagnosed according to the criteria of Kidney Disease Improving Global Outcome.[5]

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

**Exclusion criteria:**
- Increased serum creatinine, which was attributed to causes other than HIE such as hypovolemia, sepsis, or infection.
- Life-threatening congenital anomalies, inborn errors of metabolism, or preterm births.

This study was carried out after obtaining written consents from the parents of included subjects and after obtaining approval from research ethics committee of Tanta Faculty of Medicine in accordance with the Declaration of Helsinki.

**All subjects were subjected to the following:**

1. Full history taking: Focusing on gestational age, postnatal age, sex, neurological symptoms such as fits, perinatal history including mode of delivery, Apgar scoring at 1 and 5 min, and neonatal resuscitation measures.

2. Through clinical examination which included:
   - General examinations
   - Vital signs and urine output
   - Anthropometric measurements, especially body weight
   - Systemic examination
   - Neurological examination
   - Level of consciousness: whether alert, lethargic, or comatose
   - Motor system, including muscle power, muscle tone, and reflexes

3. HIE Sarnat staging system: HIE was defined as mild, moderate, or severe using the Sarnat and Sarnat staging system.[6] The assessed elements included level of consciousness, muscle tone, muscle tendon and tendon reflexes, seizures, autonomic function, and electroencephalogram description.

4. Laboratory investigations, which were carried out for all subjects (patients and controls), included:
   - Complete blood count (CBC)
   - Liver function tests
   - Serum electrolytes, including serum sodium (Na), serum potassium (K), and serum calcium (Ca)
   - Arterial blood gases (ABG) to measure PH, PaO₂, PaCO₂, and base excess
   - Serum creatinine levels by routine laboratory technique

5. Imaging radiological investigations:- Brain CAT scan that was carried out for all cases.

**Collection of blood samples:** A total of 3 mL of venous blood was taken from all studied groups. Blood samples were centrifuged at 4000 rpm for 10 min. Serum samples were separated and stored at refrigerator at –2 to –80°C until the time of laboratory assay.

**Statistical Analysis**

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0, for analysis, (Methodology, Methods and techniques, 2nd edition. New Delhi, India). According to the type of data, the following tests were performed to test differences for significance: differences between frequencies for qualitative variables and percentages in groups were compared by chi-square test and differences between mean values of quantitative variables of two parametric groups by t test. P value was set at <0.05 for significant results and <0.001 for highly significant result.[7]

**Results**

Table 1 shows demographic and clinical data of the studied patients and controls. No statistically significant difference was observed between the studied groups with regard to gestational age, weight, or sex (P > 0.05).
A statistically significant increase was observed in the patient group when compared to controls with regard to history of maternal hypertension associated with or complicating pregnancy or antepartum hemorrhage ($P < 0.05$).

No statistically significant difference was observed between the studied groups with regard to mode of delivery (normal vaginal delivery vs. cesarean section) ($P > 0.05$).

As per the Apgar score at 1 and 5 min for cases and controls, a statistically significant decrease was observed in cases when compared to controls ($P < 0.05$).

With regard to neonatal resuscitation measures for the studied groups, a statistically significant increase was reported in the use of free oxygen flow and insertion of endotracheal tube (ETT) in cases than that in controls ($P < 0.05$).

Table 2 shows the laboratory findings of the studied patients and controls including CBC, ABG, serum electrolytes, liver enzymes, blood urea, and serum creatinine levels.

Regarding clinical presentations of the studied neonates, they were classified according to Sarnat and Sarnat stages of HIE into stages I, II, and III.
Table 2: Laboratory characteristics of the studied cases and the controls

| Parameter         | Statistical parameter | Group 1 (patients) (n = 36) | Group 2 (controls) (n = 36) | Statistical test | P value |
|-------------------|-----------------------|-----------------------------|-----------------------------|------------------|---------|
|                   |                       | Mean ± SD                   | Mean ± SD                   |                  |         |
| WBCs              |                       | 14.7 ± 9.9                  | 3.4 ± 1.6                   |                  | 5.09    | 0.001  |
| RBCs              |                       | 4.1 ± 1.3                   | 5.2 ± 1.9                   |                  | 2.49    | 0.015  |
| CBC               |                       | 12.7 ± 1.1                  | 16.4 ± 1.5                  |                  | 1.4     | 0.14   |
| Platelets         |                       | 193 ± 91.9                  | 186.1 ± 60.5                |                  | 0.3     | 0.76   |
| ABG               | pH                    | 7.03 ± 0.13                 | 7.39 ± 0.03                 |                  | 11.2    | 0.000* |
|                   | PCO₂ (mm Hg)          | 30.5 ± 12.7                 | 39.2 ± 3.06                 |                  | 2.2     | 0.02   |
|                   | PO₂ (mm Hg)           | 39.5 ± 16.6                 | 37.1 ± 6.5                  |                  | 7.8     | 0.001* |
|                   | HCO₃ (mmol/L)         | 11.1 ± 2.9                  | 22.2 ± 2.1                  |                  | 12.5    | 0.001* |
|                   | BE (meq/L)            | -11.1 ± 3.5                 | 0.55 ± 0.23                 |                  | 3.9     | 0.35   |
| Serum Ca          |                       | 0.99 ± 0.14                 | 1.25 ± 0.07                 |                  | 11.28   | 0.001* |
| Serum Na          |                       | 129.6 ± 7.2                 | 134.3 ± 6.3                 |                  | 2.4     | 0.016* |
| Serum K           |                       | 4.4 ± 0.75                  | 4.5 ± 0.1                   |                  | 0.54    | 0.58   |
| SGPT              |                       | 113.5 ± 114.2               | 21.1 ± 5.2                  |                  | 3.4     | 0.002* |
| SGOT              |                       | 110.2 ± 104.09              | 20.9 ± 5.06                 |                  | 3.6     | 0.001* |
| Serum creatinine  | (mg/dL)               | 0.87 ± 0.76                 | 0.36 ± 0.21                 |                  | 2.7     | 0.01*  |
| Blood urea (mg/   | Mean ± SD             | 64.05 ± 22.7                | 27.16 ± 5.5                 |                  | 3.1     | 0.004* |
| dL)               |                       |                            |                             |                  |         |

SD = standard deviation, RBCs = red blood cells, HB = hemoglobin, BE = base excess, SGPT = serum glutamate pyruvate transferase, SGOT = serum glutamate oxaloacetate transferase

*P value <0.05 significant

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

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

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

| CAT brain       | Serum creatinine At day 7 (mg/dL) | t    | P value |
|-----------------|----------------------------------|------|---------|
| Normal          | 0.44 ± 0.15                      | 5.01 | 0.02    |
| Brain edema     | 0.51 ± 0.01                      |      |         |
| Severe ischemia | 0.73 ± 0.011                     |      |         |

SD = standard deviation

Reperfusion of previously ischemic tissue may also enhance the formation of excess oxygen free radicals (known as reactive oxygen species), which may cause damage of cellular lipids, proteins, nucleic acid, and the blood–brain barrier.[9]

In response to acute hypoxia, the fetal and neonatal cardiovascular system attempts to preserve blood flow to the brain, heart, kidney, and adrenals. Multiple organ injury including AKI occurs in 70% of infants with the diagnosis of HIE, as evidence of end-organ involvements is necessary to meet the definition of birth asphyxia.[10]

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

DISCUSSION

Perinatal asphyxia is an insult to the fetus and/or neonates because of lack of oxygen (hypoxia) and/or lack of perfusion (ischemia) to various organs. It is associated with tissue lactic acidosis and hypercapnia. The sequelae of hypoxia and ischemia may not be identical, but they are difficult to be separated clinically. Both factors probably contribute to multisystem injury.[8]

Hypoxic–ischemic injury is the most important consequence of perinatal asphyxia.[8]
and reversible. In fact, the central nervous system is often the main organ system that has residual sequelae at long-term follow-up.[11]

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

In our study, regarding brain CAT scanning, 24 (66.7%) showed no abnormal radiological findings, 4 (11.1%) had brain edema, and 8 (22.2%) had severe ischemic findings.

Our study agreed with the results of the study by Volpe,[12] which reported that infants with normal CAT scans rarely exhibit major neurological deficits on follow-up and infants with scans showing marked diffuse hypodensity are rarely normal on follow-up.

Our study disagreed with the findings of the study by Tippin et al.[13] Although CAT 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.[14]

In our study, a significant increase was observed regarding blood urea and serum creatinine levels in cases group when compared to that in control group (P < 0.05). These results were in agreement with Huang et al.[15] who found that serum urea and creatinine level were significantly elevated in their patient group with HIE in comparison to their control group. Bhantnagar et al.[16] also reported that the concentration of blood urea and serum creatinine was significantly higher in their patients who were hypoxic ischemic when compared to that in their control group. These findings were in accordance also with those of Gupta et al.[17] who found that serum creatinine and blood urea levels were significantly higher in asphyxiated newborns compared to those in control group.

Our results were in accordance with many previously published articles including those of Gopal,[18] Alaro et al.[19] and Amardiyanto et al.[20]

In this study, results of serum creatinine and blood urea levels were significantly correlated with the degree of HIE according to Sarnat and Sarnat staging as the level of serum creatinine in patient subgroups differs 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 blood urea and serum creatinine levels showed a highly significant increase with increased severity of Sarnat stages. These results were in accordance with the findings of Gupta et al.[17] who studied renal failure in asphyxiated neonates and stated that blood urea and serum creatinine levels were significantly higher in asphyxiated neonates when compared to that in the control group. A rising trend in the concentrations of blood urea and serum creatinine was also observed as HIE staging progressed, and the difference was statistically significant.

Andreoli,[21] Gharehbaghi and Peirovifar,[22] and El-Gamasy and Nassar[23] reported that HIE was one of the most prevalent risk factors for AKI in newly born infants.

In our study, a statistically significant increase was observed in serum creatinine levels in cases with abnormal CAT radiological findings of the brain when compared with those without brain radiological abnormalities by CAT scan and a significantly increase was observed in serum creatinine levels in cases with severe ischemia when compared with those with brain edema as CAT findings of the brain.

Our results were in accordance with the study by Park et al.,[24] who studied correlations between the severity of HIE and the development of acute renal failure (ARF) in asphyxiated neonates and found that the greater the degree of HIE, the higher incidence of ARF.

**Conclusion**

Serum creatinine levels correlate with the severity of HIE as serum creatinine levels significantly increased with the increase in the severity of HIE according to Sarnat and Sarnat staging. A statistically significant difference was observed among serum creatinine levels regarding CAT radiological findings of brain. This means that a marked elevation in serum creatinine levels correlate with the severity of HIE by CAT findings of brain. So higher serum creatinine levels than normal for age were an indicator for the severity of HIE.

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**Conflicts of interest**

There are no conflicts of interest.

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