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Levels of liver enzymes in full-term neonates with perinatal asphyxia

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Abstract – Perinatal asphyxia is a transient interruption of oxygen availability that implies a risky metabolic challenge, even when the insult does not lead to a fatal outcome. In order to assess liver enzymes in neonates with perinatal asphyxia, and to correlate between the rise in enzymes to the severity of asphyxia. A case control study was carried out to measure serum liver enzymes in (43) full term neonates with perinatal asphyxia, aged 1-10 days who were admitted to the neonatal care unit. Fifty- seven neonates were selected as a control group. Patients were assessed at birth for their crying, breathing, Apgar score, gestational age, and underwent full physical and neurological examination. Assessment of the staging of asphyxia was done according to the Sarnat staging system. Serum liver enzymes; alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were measured for patients and controls. Enzymes levels beyond +2SD above the mean of control group were regarded as high. Mean level of ALT, AST and ALP for asphyxiated neonates were (67.23±4.61, 89.02±7.99, 294.26±22.80) respectively and those for control group (21.60±3.71, 40.91±2.44, 201.49±11.63) respectively, the differences were statistically significant (p-value = 0.000). The rise in liver enzymes was related to the severity and staging of perinatal asphyxia in form of Apgar score and Sarnat staging, with statistically significant result, p-value < 0.05. liver enzymes were shown to be elevated in perinatal asphyxia and their assessment is important as a predictor for asphyxia.

Keywords: Apgar, asphyxiated, neonates, Sarnat, staging.

1. Introduction

Perinatal asphyxia is a transient interruption of oxygen availability that implies a risky metabolic challenge. The guidelines of the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) consider all of the following criteria in diagnosing asphyxia: (1) profound metabolic or mixed acidemia (pH <7.00) in umbilical artery blood sample, if obtained. (2) Persistence of an Apgar score of 0–3 for longer than 5 minutes. (3) Neonatal neurologic sequelae (e.g., seizures, coma, hypotonia). (4) Multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines). [1] Hypoxic-Ischemic Encephalopathy (HIE) is the most sever result of perinatal asphyxia. [2] Sarnat and Sarnat staging is used for grading of HIE. Depending on the neurobehavioral signs, neonates were divided into three stages: [3] Mild (stage I), moderate (stage II), or severe (stage III). HIE is commonly diagnosed using physical examination, which evaluates the level of consciousness, neuromuscular control, tendon reflex, pupils, heart rate, bronchial and salivary secretions, gastrointestinal motility, presence or absence of myoclonus or seizures, electroencephalography findings, and autonomic function. [4] A 5 minutes Apgar score of 7-10 designed as reassuring, a score of 4-6 as moderately abnormal, and score of 0-3 as low in term infant and considered one of the first indications of encephalopathy, correlated with neonatal mortality but does not predict individual neurological outcome. [5] The neonate is diagnosed as having perinatal asphyxia if he has features of HIE along with one of the following criteria:

(1) Apgar score ＜7 at 1 minute of life. (2) History of delayed cry (5 minutes after birth) or no cry after birth (the guidelines laid down by the National-Neonatal -Perinatal Database network of India).[6] Perinatal

asphyxia leads to a chain of adaptive responses to curtail the body's oxygen requirement, in an attempt to tide over the hypoxic crisis. One such mechanism is called "diving reflex" or redistribution of left ventricular output in favor of more vital organs such as brain, heart, and adrenals at the expense of reduced blood flow to non-vital organs such as kidneys, lungs, gastrointestinal tract, and other abdominal viscera.[6] Multi organ dysfunction is a natural consequence of this defense mechanism. The most frequently affected organs are lungs and liver.[7]

Hepatic dysfunction in perinatal asphyxia**:** Liver cell injury commonly occurs after perinatal asphyxia. It is represented as an early, abrupt, and transient (within 24–72 hours after insult) increase in aminotransferases (AST), (ALT) and alkaline phosphatase (ALP). Later on, the peak aminotransferase level returns to near normal within 10 days. The prognosis of hypoxic hepatitis itself is safe, and it rarely progresses into complete hepatic failure. Because of improvement in medical care, the clinical entity of liver involvement is being increasingly recognized. [8]

Serum level of liver enzymes may increase either due to hepatocyte death or to an increase in cell membrane permeability which allows efflux of enzymes into the blood.[6] Regardless of the underlying mechanism, whenever hepatic microcirculation decreases below a critical threshold, cellular ischemia is induced, and this leads to hepatic injury and dysfunction. Liver injury is commonly recognized under the terms shock liver or hypoxic hepatitis. [9]

Hypoxic hepatitis (H.H) is characterized by centrilobular liver cell necrosis as consequence of hypoperfusion with subsequent ischemia and passive congestion of the liver, severe systemic arterial hypoxemia, and/or impaired hepatic oxygen extraction.[10] Diagnosis of HH is generally simple if the clinical setting and biological pattern are suggestive. Liver imaging is of little practical interest in the diagnosis of HH. It will simply show features related to passive congestion but not to liver cell necrosis.[11] Liver biopsy is not required for the diagnosis of HH.[12] The duration of HH has a significant impact on outcome. Clinicians should therefore undertake efforts to avoid occurrence and progression of this disease as early as possible to improve outcome in patients with HH.[12]

This study was carried out to assess liver enzymes; ALT, AST and ALP in neonates with perinatal asphyxia and to study the relation of enzyme elevation to the severity of asphyxia.

2. Methods

A case-control study had been carried out in the first neonatal care unit in Basra Maternity and Children Hospital from October 2015 to April 2016. A total of 43 asphyxiated full-term neonates aged 1-10 days, 26 males and 17 females were enrolled as study group. The diagnosis of perinatal asphyxia was based on the presence of features of hypoxic ischemic encephalopathy (HIE) along with one of the following criteria: (1) Apgar score ＜7 at 1 minute of life, (2) history of delayed cry (5 minutes after birth) or no cry after birth (the guidelines laid down by National-Neonatal Perinatal database network of India).[6] The severity of asphyxia was assessed by Sarnat & Sarnat staging system. Exclusion criteria include causes other than ischemic encephalopathy like a major congenital anomaly, sepsis, congenital infection, hemolytic condition, hemorrhagic shock, primary hepatobiliary disease and the premature neonates.

Another 57 healthy full term- neonates, (30) males and (27) females who were attending outpatient clinic for checking or with mild illness like colic or oral thrush were enrolled as control group after taking consent from their parents and were matched for age, sex, body weight and gestational age.

A special Questionnaire was designed for the purpose of the study to collect neonatal data. All patients were assessed at birth for their crying, breathing, Apgar score at 1,5,10 minutes, assessment of gestational age and

physical examination, assessment according to Ballard Scoring System (Carlo and Ambalavanan, 2011). Other assessment includes full neurological, cardiopulmonary and abdominal examination.

A blood sample of 2 milliliters was taken from each neonate in patient and control groups to estimate serum ALT, AST and ALP. Enzymes levels beyond +2SD above the mean of control group were regarded as high. Elevated levels of enzymes were assessed in relation to selected neonatal factors.

The normal values of the liver enzymes were estimated according to values measured for healthy neonates recruited in this study and are presented by mean ± 2 standard deviation (SD) [13] as shown in table (1)

Table 1: Normal values of liver enzymes of control group

Parameter	Control group	Normal range
ALT(IU/L)	21.60±3.71	(14.18-29.02)
AST(IU/L)	40.91±2.44	(31.23-45.79)
ALP(IU/L)	201.49±11.63	(178.23-224.75)

High enzyme level is defined as a value more than 2 SD from the mean.
Statistical analysis was done using SPSS program version 20. Data were expressed by mean and Standard Deviation. A comparison of proportions was performed using Chi-Square test. The t-test and ANOVA were used for quantitative comparison of variables. For all tests p-value of <0.05 was considered as statistically significant.

3. Results

Forty- three newborns with perinatal asphyxia (study group) and fifty -seven healthy newborns (control group) were matched for age and sex as demonstrated in Table (2)
The values of (ALT, AST, ALP) are assessed in both patients and control, categorized in two groups; normal and high, and were compared between patients and control group as shown in table (3a and 3b). The mean value of all liver enzymes (AST, ALT, ALP) in asphyxiated neonates were higher when compared to the control group.

3.1 Effect of severity and staging of asphyxia on liver enzymes:

Patients who had elevated levels of enzymes were assessed in relation to severity of asphyxia which was represented by Apgar score and Sarnat staging system. Table (4) demonstrated that the levels of all enzymes were higher among neonates with low Apgar score and in stage three of asphyxia.

Table 2: Selected characteristics of patients with perinatal asphyxia and control group

Variable		Patient (N=43) N. (%)	Control (N=57) N. (%)	P –value
Age (days)	≤7	31 (72.10)	42 (73.70)	*0.859
	7-10	12 (27.90)	15 (26.30)	
Sex	Male	28 (65.10)	31 (54.40)	*0.280
	Female	15 (34.90)	26 (45.60)	
B.WT (kg)	<2.5	9 (20.93)	10 (17.50)	**0.864
	2.5-4	32 (74.42)	40 (70.22)	
	>4	2 (4.65)	7 (12.28)	
Growth Status	LGA	14 (32.55)	18 (31.59)	*0.789
	AGA	17 (39.53)	26 (45.61)	
	SGA	12 (27.97)	13 (22.80)	

GA	37-38	36 (83.72)	49 (85.96)	**0.179
	39-40	3 (6.97)	7 (12.28)	
	>40	4 (9.31)	1 (1.76)	

*Chi-square was used **Fisher exact was used GA=Gestational age

Table 3a: Liver enzymes values in patients and control Group

Variable	Patient (Mean ± SD)	Control (Mean ± SD)	P – value
ALT(IU/L)	67.23±4.61	21.60±3.71	0.000
AST(IU/L)	89.02±7.99	40.91±2.44	0.001
ALP(IU/L)	294.26±22.80	201.49±11.63	0.000

Table 3b: Percentage of elevated liver enzymes in patients and controls

Liver enzymes		Patient (N.=43)		Control (N.=57)		P-value*
		(Mean ± SD)	N. %	(Mean ± SD)	N. %	
ALT (IU/L)	Normal	24.33±5.03	5 (22.4)	21.06±4.54	53 (94.73)	0.0001
	High	73.66±25.79	38 (77.6)	51.82±54.59	4 (5.27)	
AST (IU/L	Normal	39.00±1.41	12 (31.1)	40.79±2.045	52 (91.22)	0.0001
	High	111.16±44.6	31 (68.9)	68.64±12.63	5 (8.78)	
ALP (IU/L)	Normal	206.38±9.95	19 (40.0)	198.89±13.72	53 (92.98)	0.0001
	High	399.58±112.43	24 (60.0)	312.19±77.12	4 (7.02)	

*Chi-square test

Table 4: Elevated liver enzymes in relation to severity of asphyxia

Variable		ALT Mean± SD	p-value	AST Mean± SD	p-value	ALP Mean± SD	P-value
APGAR SCORE	≤3	97.71±22.07	* 0.000	99.90±47.10	* 0.003	332.09±87.84	* 0.017
	4-6	45.47±29.26		48.62±40.02		223.20±45.24	
STAGE 1		56.45±12.67	** 0.001	52.42±40.91	** 0.018	202±23.56	** 0.004
STAGE 2		111.10±31.78		106.25±58.45		362.17±63.50	
STAGE 3		156.13±13.56		137.91±31.76		426.27±35.02	

* t-test was used ** ANOVA was used A.S 5 =Apgar score at five minutes

4. Discussion

It is well known that perinatal asphyxia in newborn can cause hepatic hypoxic injury. The serum activity of AST and ALT is one of the more specific parameters of liver cell injury.[14] The current study had revealed that the mean values of ALT, AST, and ALP in asphyxiated neonates were significantly higher than those of control group. These results were in agreement with Islam et al in Bangladesh [14], Paliwal et al in India [15] and with Chhavi N et al in Korea. The rise in transaminases is indicative of liver cell dysfunction, either due to hepatocyte necrosis or due to changes in cell permeability that may occur in perinatal asphyxia.[14] It was found that most patients had elevated levels of all enzymes in comparison to control, less than10% of control group had elevated enzymes, this had agreement with Bugeac N et al in Haifa, they concluded that the isolated elevation of serum aminotransferases in apparently healthy, thriving infants is mostly a benign condition that usually resolves within a year. The etiology is unclear but may be related to some unknown viral etiology.[16]

It was observed that elevation of the liver enzymes was related to severity of asphyxia, all liver enzymes showed higher values in stage three, this is consistent with that found by Islam et al in Bangladesh[14] and with Karlsson M et al in Sweden[13] and Paliwal et al in India[15] while a study by Chhavi N et al in Korea[7] revealed that the degree of serum liver enzymes had no relation with the severity of HIE.

Elevated liver enzymes ALT, AST and ALP were found to be higher in babies with lower Apgar score ≤3 at 5 minutes, this indicates a positive relation between the severity of asphyxia and elevation of liver enzymes, this is consistent with Choudhary M et al in India[8] who found elevated levels of ALT, AST and ALP in patient diagnosed with sever asphyxia with low Apgar score ≤3 at 5 minutes, this may be explained by severity of hypoxemia in asphyxiated babies which adversely affects the liver as part of multi-system insult, may be so damaged (Shock liver) that it may not provide its basic functions[17].

5. Conclusions

Liver enzymes were shown to be elevated in perinatal asphyxia and their assessment is important as a predictor for asphyxia. Other studies are recommended to support our findings.

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