

## Liver impairment among neonates with moderate to severe asphyxia

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### Abstract

**Background and Objectives:** Perinatal asphyxia may cause severe damages in different organs such as kidneys, lungs, liver and most importantly CNS. The current study aimed to evaluate and compare the prevalence of liver impairment among asphyxiated and normal neonates.

**Methods:** A retrospective case-control study was carried out in a referral pediatrics Hospital (Iran- from 2013 to 2015). Term and preterm asphyxiated neonates born in hospital were registered as the case group. Serial laboratory tests including CBC, Creatinine, BUN, Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>+</sup> and blood sugar were done. ALT, AST and ALP were also measured at day of third to fifth of life. Healthy neonates who admitted due to hyperbilirubinemia were also considered as the controls and their liver enzymes were checked at day of third to fifth of life. All participants' demographic data and laboratory findings were extracted from medical records. Liver impairment by assessing liver enzymes was compared between case and control groups. The level of significance was considered as  $p < 0.05$ .

**Results:** Forty-nine asphyxiated neonates as the case and 20 icteric neonates as the control group entered the study. Of all asphyxiated neonates, 23 cases (46.9%) showed seizure, 25 (52.1%) type II and 23 (47.9%) type III Hypoxic-ischemic encephalopathy. Seven (10.1%) asphyxiated neonates died. More neonates in control group had gestational age  $\geq 37$  weeks ( $p < .05$ ). Mean and median serum ALT in case group was significantly higher than controls ( $p < .05$ ). A significant difference was also observed between two groups with regard to mean serum ALP ( $p < .05$ ). Elevated ALT, AST and ALP were more frequent in the case group in compare to the control group.

**Conclusion:** Elevated ALT and ALP in 3-5 days of age can be utilized as possible predictors of perinatal asphyxia.

**Keywords:** Birth asphyxia, Neonate, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP)

### Background

Perinatal asphyxia is defined as insufficient blood gas exchange during the birth process resulting hypoxia, hypercarbia and metabolic acidosis (1). Hypoxic-ischemic encephalopathy (HIE) due to asphyxia is one of the most important causes of neonatal mortality (2). The frequency of perinatal asphyxia is reported 1-1.5% in devel-

oped countries with advanced obstetric and neonatal health care system (3).

The signs of perinatal asphyxia are metabolic or mixed acidosis in umbilical cord blood sample, prolonged Apgar score 0-3, neurologic manifestations including seizure or hypotonic comma and multi organs involvements. Prolonged antenatal acidosis (more than one hour), fetal bradycardia (fetal heart rate  $< 60$  beat/min), sustained apgar

score  $\leq 3$  for 10 minutes, requirement of positive pressure mechanical ventilation for more than one minute, delayed crying, burst suppression in EEG or  $\alpha$ EEG, Suppressed background pattern and seizure occurrence at first 12-24 of life are also identified as other criteria (1).

Perinatal asphyxia may cause severe damages in different organs such as kidneys, lungs, liver, and most importantly CNS. However, the “diving reflex” preserves vital organs perfusion (brain and heart) at the expense of declined blood flow to other organs like kidneys or liver (4). Hepatic involvement is commonly found in the asphyxiated subjects (5). The physiopathology of liver impairment due to perinatal asphyxia is similar to that in ischemic hepatitis (6). The correlations between liver impairment, severity of the asphyxia and HIE were shown by previous reports (2,7). Islam et al. indicated significant differences between mean liver enzymes of asphyxiated and normal neonates. They also found that the elevation of liver enzyme was proportional to the severity of hypoxia (8).

Prenatal asphyxia is responsible for 25% of mortality and 78% of morbidity rates (9). Altered liver enzymes are observed in damaged hepatocytes due to asphyxia (10). The current study aimed to evaluate and compare the prevalence of liver impairment by assessing liver enzymes among asphyxiated and normal neonates which would be of value in implementing strategies to decrease morbidity and mortality rate.

### Methods

A retrospective case-controlled study was carried out in the neonatal unit of Akbarabadi Hospital affiliated to Iran University of Medical Sciences (Tehran-Iran) from 2013 to 2015. Term and preterm asphyxiated neonates born in hospital were registered as the case group. Perinatal asphyxia and its severity were determined by an expert neonatologist. Exclusion criteria were congenital anomalies, hemorrhagic shock, sepsis and hepatic dysfunction. All subjects at birth were resuscitated and underwent positive pressure ventilation by mask, bag or tracheal intubation. Supportive therapies including IV therapy, anticonvulsive drugs and correction of electrolyte imbalance were also implemented. Serial laboratory tests including CBC, Creatinin, BUN,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^+$  and blood sugar were done. ALT, AST and ALP were also measured at day of third to fifth of life. Admitted healthy neonates due to hyperbilirubinemia who their liver enzymes at day of third

to fifth of life had been measured (based on neonatologists' order) were considered as the controls.

Asphyxia was considered as Apgar score of 0 to 3 for longer than 5 minutes. Hypoxic-ischemic encephalopathy was defined according neurologic findings; changes in muscular tonicity, sensorium and deep tendon reflexes, absence of primitive reflexes, seizure as well as mydriasis. Severity of HIE (Stage I, II & III) was evaluated based on Sarnat & Sarnat staging. Liver impairment criteria were ALT  $>50$  u/l, AST  $>140$  u/l, ALP  $>420$  u/l.

All participants' demographic data and laboratory findings were extracted from medical records. Finally, liver impairment by assessing liver enzymes was compared between case and control groups. Recorded data were analyzed by software package SPSS version 20. Frequency was reported by mean $\pm$ SD. Median test, Pearson Chi-Square, Kolmogorov-Smirnov and t-student tests were used to analyze the correlations between variables. The level of significance was considered as  $p < 0.05$ . With the proposed sample size of 219, the study had a power of 75% and an alpha error of 0.05. Our study was approved by the institutional review board of Iran University of Medical Sciences according Helsinki declaration. Our gathered data were confidential and no extra cost was constrained on our participants.

### Results

Forty nine asphyxiated neonates as the case and 20 icteric, under phototherapy neonates as the control group entered the study. In the case group, 69.38% were male and 65.30% were born by cesarean section while in the control group 75% were male and 75% were born by cesarean section. Of all asphyxiated neonates, 23 cases (46.9%) showed seizure, 25(52.1%) type II and 23 (47.9%) type III Hypoxic-ischemic encephalopathy. Seven (10.1%) asphyxiated neonates died. Detailed data are shown in Table 1.

No significant differences were seen between two groups regarding to demographic data except from gestational age; neonates in the control group were older for a week ( $37 \pm 2.44$ ,  $36.45 \pm 1.31$ ,  $p < .05$ ).

As shown in Table 2, mean and median serum ALT in the case group were significantly higher than controls ( $p < .05$ ). A significant difference was also observed between two groups with regard to mean serum ALP ( $p < .05$ ) (Table 2). Elevated ALT, AST and ALP were more frequent in case

Table 1. Demographic data of all participants.

Variables	Case N=49	Control N=20	p value
Male/female	34/15	15/5	.649
Mean birth weight (gr)	2863.9±569.64	2901.9	.94
Mean gestational age (weeks)	37±2.44	36.45±1.31	0.348
gestational age ≥37 weeks	22 (44.89%)	15 (75%)	.028
Mode of delivery Cesarean/ normal delivery	32/17	15/5	.43

Table 2. Comparison of liver enzymes between both groups

Variables (IU/L)	Case	Control	p value
Mean serum AST	102.86 ± 109.55	68 ± 37.18	.183
Mean serum ALT	45.31 ± 45.19	16.25 ± 6.78	.00
Mean serum ALP	433.80±164.988	309.63 ± 177.88	0.033
Median Serum AST	64 (48-113.25)	(40.25-100) 47	0.442
Median Serum ALT	35(14.75-49.25)	15 (10.75-22.75)	.00
Median Serum ALP	(308-535) 452	(35-444) 385	0.177

group in compare to control group (Tables 3, 4).

### Discussion

Birth asphyxia as a multi system disorder can cause hepatic dysfunction. The serum levels of AST, ALP and ALT are specific markers of injured Hepatocytes (14) and can be utilized as possible predictors of perinatal asphyxia from point of severity or timing of hypoxic events (5).

Based on present study mean serum ALT in the asphyxiated babies was significantly higher than controls. Many studies pointed to the efflux of liver enzyme in to the blood due to hepatocyte apoptosis or impaired cell membrane permeability (4,11,12). Choudhary et al showed increased ALT levels a result of asphyxia (5). Chhavi et al. also found that singleton term neonates with birth asphyxia had higher serum levels of ALT in compare to controls (4). This abrupt rise in levels of hepatic enzymes is shown immediately after hypoxia, with a peak during 1-3 days and returning to normal range after 7-10 days (11).

The mean ALT levels in this study was 45.31±45.19 IU/L. Increased ALT of more than 40 IU/L was shown in other studies (16,17). Godambe et al. also noted this range between 35.3 ± 28.8 IU/L to 65.6 ± 33.2 IU/L in mild to severe asphyxiated neonates (13). The mean ALT of asphyxiated babies and normal babies were reported 88.8±43.5 U/L and 27.5±8.5 U/L, respectively by Paliwal et al. (14). It is supposed that these different ranges are due to differences in newborn's age and cell membrane permeability due to immatu-

ity, the severity of asphyxia, age at laboratory assessment or Laboratory errors.

Our results also showed a significant difference between two groups regarding mean serum ALP. In accordance to our results Islam et al. showed a significant elevated serum ALP level among asphyxiated neonates; this correlation between ALP and the severity of asphyxia was also significant ( $p < 0.001$ ). Mean serum ALP in our case group was 124.17 IU/L higher than in controls while based on Islam et al. study, this range was 161.39 IU/L (8).

We could not find any significant difference between two groups' AST. However Choudhary et al. revealed a significant difference between case and control groups in terms of plasma AST levels ( $p < 0.001$ ) (5). Islam in another study demonstrated that serum AST, ALT and ALP levels in 70 full term asphyxiated neonates were significantly

Table 3. Liver impairment based on ALT &gt;50 u/l, AST&gt; 140 u/l, ALP&gt;420 u/l

	Case	control
AST >140	8(17.4%)	0 (0%)
ALT >50	11 (23.9%)	0 (0%)
ALP >420	24 (55.8%)	3 (27.3%)

Table 4. Liver impairment based on ALT and AST &gt;100 u/l

	case	control
AST > 100	14(30.4%)	3(15%)
ALT > 100	7(15.2%)	0(0%)

different from those in 50 age and sex matched healthy neonates ( $p < 0.001$ ) (15).

Among our case group 17.4% demonstrated rise in AST, 23.9% in ALT and 55.8% in ALP while these ranges in another study was reported 52.9%, 87.1%, and 32.9% , respectively (15).

Although neonates in the control group were older, this difference was not notable. Neonates in the control group were older than their counterparts in the case group for only a week.

### Limitation

Our study has some limitations; we measured enzymes once and did not follow our subjects after 3-5 days. Other liver enzymes and indices were not assessed. However such limitations were due to ethical considerations to limit neonates' blood sampling. The number of neonates in the control group was so limited; as our study was a retrospective investigation, we had few medical records of icteric neonates who their liver enzyme were assessed and recorded. Further studies with larger sample size are strongly suggested that could provide some informative and beneficial data.

### Conclusion

Results of this study indicated that ALT and ALP in 3-5 days of age significantly elevated in perinatal asphyxia due to pathological changes in the liver. These factors can be utilized as possible predictors of perinatal asphyxia for sooner and better diagnosis, prevention and treatment.

*Conflicts of interest:* None declared.

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