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Research Article

Early Hepatic Dysfunction in Asphyxiated Full Term Newborns

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Abstract

Parental asphyxia is one of the most devastating complications associated with birth process in which dramatic transient elevation in serum concentrations of hepatic enzymes occurs in some patients.

Objectives: To evaluate the temporal hepatic enzyme pattern in asphyxiated full term newborn infants.

Methods: This study was conducted on sixty asphyxiated full term neonates recruited from Neonatal Intensive Care Unit [NICU], children's hospital, Ain-Shams University Hospital.

Inclusion criteria: was Apgar score < 7 at 5 minutes after birth, gestational age of more than 36 weeks, mild, moderate or severe Hypoxic Ischemic Encephalopathy [HIE] as defined by Sarnat and Sarnat, 1976. Plus one of the following should be present: Resuscitation with more than 3 minutes of positive pressure ventilation before Table spontaneous respiration, umbilical cord arterial pH < 7.20.

Exclusion criteria: Primary diseases of liver or bacterial sepsis or potentially hepatotoxic drugs therapy. Thirty healthy newborn infants served as controls.

Results: Transient liver dysfunction occurred in 70% of asphyxiated cases as regard ALT and 83% as regard AST, 60% of cases followed temporal enzyme pattern as regard ALT. The highest increase in the enzymes was observed after 3 days of delivery and then normalized after 6-12 days.

Conclusion: Severe birth asphyxia can cause reversible hypoxic hepatitis and furthermore, temporal pattern of amino transferases, despite high vascularity of the liver.

Introduction

Asphyxia is an insult to the fetus or newborn due to lack of oxygen or lack of perfusion to various organs [1]. Parental asphyxia is one of the most devastating complications associated with birth process [2] and it is an eventuality having far-reaching effects in the neonatal period [3]. The overall incidence of perinatal asphyxia is varying from 1.0 to 1.5% at several centers [3]. Hypoxia can cause damage to almost every tissue and organ. In response to hypoxic- ischemic insult to the fetus, a series of protective reflexes occur to prevent damage to more vital organs [brain, heart and adrenals] at the expense of lesser vital organs [kidneys, lungs, gastrointestinal tract, liver and spleen] by an attempt to redistribute available blood flow [3]. The most sensitive organs to asphyxia are those with a high energetic demand and with an active metabolism; as central nervous system, myocardium and liver [4]. Hepatic involvement is often found in the subjects as it is highly involved in so many metabolic processes [3]. This entity is variously termed "shock liver" or ischemic hepatitis. The condition is appropriately termed hypoxic hepatopathy [1] in which dramatic transient elevation in serum concentrations of hepatic enzymes [amino transferases [AST and ALT] and LDH plasma activity] occurs [5]. Later on, the peak amino transferases level returns to normal within 10 days. The prognosis of hypoxic hepatitis itself is good, and it rarely progresses into fulminant hepatic failure [6]. Severe birth asphyxia frequently induces multi organ failure with cardiovascular, renal, cerebral and hepatic damage [7]. This work aimed to elucidate the presence of transient liver involvement in birth asphyxia and to assess the severity of hepatic dysfunction in relation to HIE grading of asphyxiated newborns.

Materials and Methods

This cross-sectional controlled study was conducted on sixty asphyxiated full term neonates recruited from Neonatal Intensive Care Unit [NICU], Children's Hospital, Ain-Shams University, Cairo.

Neonates included in the study had the following criteria: Apgar score < 7 at 5 minutes after birth, gestational age of more than 36 weeks, with mild, moderate or Severe Hypoxic Ischemic Encephalopathy [HIE] as defined by Sarnat and Sarnat, [1976] [8]. In addition to the previous criteria, one of the following should be present: Resuscitation with more than 3 minutes of positive pressure ventilation before Table spontaneous respiration, umbilical cord arterial pH < 7.20 [9].

In HIE stage I, no seizures are experienced, and the EEG pattern is normal. The infant is conscious, but irritable and jittery, tachycardic and has dilated pupils as signs of increased sympathetic activity. Reflexes are normal or increased.

In HIE stage II, seizures are usually seen within 12 hours after birth, and the EEG is abnormal. The infant responds slowly to stimuli, and spontaneous movement is scarce. Lower heart rate and constricted pupils are examined. The infant is hypotonic and lethargic.

In HIE stage III, seizures are frequently seen but are more prolonged and resistant to treat with anticonvulsants. The EEG is abnormal with decreased background activity. The infant is in stupor with neither reflexes, nor spontaneous movements.

None of the included infants had primary diseases of liver or bacterial sepsis or congestive heart failure or used potentially hepatotoxic drugs therapy. 30 cases of healthy newborn infants with Apgar score > 7 at 5 minutes served as control.

All subjects were subjected to full medical history laying stress on antenatal, natal and postnatal history especially history of anesthesia, antepartum hemorrhage, intrauterine fetal distress and drug intake by mother and infant. Full clinical examination laying stress on Apgar score, conscious level, muscle tone, suckling, more reflexes, abdominal examination, and heart rate to determine the stage of HIE.

Verbal consent was obtained from the parents or guardians of the neonates who served as subjects in the study. The study protocol gained agreement from the local Ethical Committee of Pediatric Hospital, Faculty of Medicine, Ain-Shams University.

Laboratory assessment

Both the asphyxiated group and the controls were subjected to the following laboratory investigations: Serum AST, ALT, GGT, serum albumin, serum bilirubin [total and conjugated], International Normalized Ratio [INR] and Hemoglobin. All the previous parameters were measured on postnatal days 1, 2 and 3 and once between day 6 and 12.

Sample collection

The samples were collected from a venous or arterial umbilical catheter or during venipuncture.

All biochemical parameters of liver function were done. Both AST [normal value 35-140 U/L] and ALT [normal value 6-50 U/L] were done using colorimetric determination of activity according to Reitman and Frankel method. LDH [normal value 160-450 U/L], GGT [normal value 0-30IU/L]. Total bilirubin [normal value 0.3-1.9mg/dl] and direct bilirubin [normal value 0-0.3gm/dl. Albumin was done using colorimetric method [Doumas method] [normal value 2.5-3.6 gm/dl]. International Normalized Ratio INR [normal value 1.1-1.2]. Hemoglobin was measured by cyano hemoglobin method. All parameters were measured postnatal days 1, 2, 3, and once between 6 and 12 days in both cases and control groups.

Statistical Analysis

Analysis of data was done by IBM computer using SPSS [Statistical program for social science version 12]. Chi-square test [χ^2] was used to compare qualitative variables between two independent groups. Unpaired t-test [student's t-test] was used to compare quantitative variables between two independent groups. Pearson correlation co-efficient test [r-test] was used. p-Value > 0.05 insignificant, $p < 0.05$ significant, p <0.01 highly significant.

Results

Demographic data

Mean gestational age of the study group was 38.6±1.3 weeks and that of the controls was 38.9±1.1weeks with no statistically significant difference between them [p-value> 0.05]. The Apgar score of the study group at 5 minutes after birth was 4.6±1.3 minutes and that of the controls was 8.5±1.3 minutes with a highly significant statistical difference detected between them [p-value<0.01].

Regarding the mode of delivery; 10 cases out of 60 [16.7%] were delivered by Normal Vaginal Delivery [NVD], and 50 cases [83.3%] by Caeserian Section [C/S], while in the control group; 18 cases out of 30 [60%] were delivered by NVD, and 12 out of 30 [40%] by C/S. Thirty two of studied cases [53%] suffered from intrapartum asphyxiating events; 20 [33%] had decreased fetal movement in last 24 hours before labour, 16 [26.6%] had abnormal fetal heart pattern, 12 [20%] abruption placenta, and 6 [10%] had prolonged labour, and 28 cases out of 60 [47%] had inconclusive obstetric history.

Among the sixty studied neonates, 34 cases [56.7%] had positive Meconium-Stained Amniotic Fluid [MAF], 24 cases [40%] had stage 1 HIE, 18 cases [30%] had stage 2 HIE and 18 cases [30%] had stage 3 HIE, while 26 cases [43.3%] had negative Meconium-Stained Amniotic Fluid [MAF].

ALT and AST

The highest increase in ALT in relation to baseline was observed at 49-72 hours [3rd postnatal day] being 146±75 IU/ml, which then decreased below the baseline level at 144-288 hours [6-12 days] to become 69.8±20 IU/ml [p< 0.01]. The highest increase in AST was observed at 49-72 hrs [3rd postnatal day] being 160±81 IU/ml, which then decreased below the baseline level at 144-288 hours [6-12 days] to become 69.8±20 IU/ml [$p < 0.01$]. The same pattern was observed with LDH in cases of the study.

Among the sixty asphyxiated newborns, [42 cases] 70% had elevation in serum ALT levels and [50 cases] 83% had elevation in serum AST level and [36 cases] 60% followed temporal enzymatic pattern for ALT while [34 cases] 56.7% followed temporal enzymatic pattern for AST.

GGT and bilirubin

A significant increase in GGT above the baseline was observed at 25-48 hours [2nd postnatal day] [9.8± 2.6] [$p < 0.05$], while non-significant increase in GGT was observed at 49-72 hours [3rd postnatal day] [10± 1.8] and 144-288 hours [6-12 days postnatal] [9.9± 1.6] [$p > 0.05$].

There was a highly significant increase in total and direct bilirubin at 25-48 hours [2nd day] [4.8± 1.8] and 49-72 hours [3rd day] [5.2± 2.5] in comparison to baseline level [3.7± 0.9] [$p < 0.01$].

Hemoglobin level gradually decreased upto 72 hours [13± 1.8] follow up with highly significant change in comparison to baseline

Table 1: Correlation between hepatic enzymes changes and HIE stage among the studied cases.

Variables	r	p-value
ALT(IU/L)	0.89	< 0.01**
AST(IU/L)	0.9	< 0.01**
LDH(IU/L)	0.69	< 0.01**
GGT(IU/L)	0.28	> 0.05

ALT: Alanine Amino transferase, **AST:** Aspartate Amino transferase, **LDH:** Lactate Dehydrogenase, **GGT:** Gamma Glutamyl Transferase.

Table 2: Relation between different enzymes versus MAF among the studied cases.

Variables	MAF –ve	MAF +ve	t	p-value
ALT(IU/L)	70±27	108±24	4	<0.01**
AST(IU/L)	96±15	111±30	1.6	>0.05
LDH(IU/L)	869±83	904±211	0.6	>0.05
GGT(IU/L)	8.7±2	9.9±2	1.5	>0.05

p<0.01**, p>0.05: non-significant, **ALT:** Alanine Aminotransferase, **AST:** Aspartate Aminotransferase, **GGT:** Gama Glutamyl Transferase, **MAF:** Meconium- Stained Amniotic Fluid.

level [15± 1.8] [$p < 0.01$]. Hemoglobin level then started to increase again after 72 hours [13.6± 1.6] follow up with highly significant change in comparison to the baseline [$p < 0.01$].

There was a highly significant difference between cases and controls concerning all laboratory variables [$p < 0.01$], except for serum albumin, GGT and hemoglobin levels, where a non-significant difference was detected [$p > 0.05$].

There was a rising trend in concentration of mean ALT and AST as staging of neonates progressed from HIE stage 0 to HIE stage III. There was a highly significant positive correlation between each of ALT, AST, LDH and the stage of HIE [r= 0.89, $p < 0.01$] [r= 0.90, $p<0.01$] [r= 0.69, $p <0.01$] respectively. as shown in table (1). Thus, hepatic enzymes changes correlated with HIE stage of asphyxia , but the change is transient and nonspecific, so it is debatable that hepatic enzymes can be used for diagnosis of neonatal hypoxia.

Also, there was a highly significant positive correlation between each of ALT, AST and INR [r= 0.93, $p < 0.01$] [r= 0.84, $p <0.01$] respectively also a highly significant negative correlation between each of ALT, AST and the hemoglobin level [r= -0.51, $p < 0.01$] [r= -0.50, $p <0.01$] respectively and a significant negative correlation between LDH and hemoglobin level [r= -0.40, $p < 0.05$]. Also, there was a highly significant positive correlation between each of ALT, AST and the age of spontaneous breathing [r=0.55, $p < 0.01$] [r=0.62, $p <0.01$] respectively and a highly significant negative correlation between each of ALT, AST and the Apgar score [r= -0.87, $p < 0.01$] [r= -0.86, $p <0.01$] respectively. A non- significant positive correlation was found between the different enzymes and the gestational age [$p > 0.05$].

ALT was found higher among positive Meconium- Stained Amniotic Fluid [MAF] [108 ± 24] in comparison to Meconium-Stained Amniotic Fluid [MAF] negative cases [70 ± 27], with highly significant difference between them [$p < 0.01$]. On the other hand, there was non-significant difference between MAF positive and negative neonates as regards other variables as shown in table (2).

Results also showed a non-significant difference regarding different studied enzymes [ALT, AST, LDH, GGT] with changing the mode of delivery [NVD or C/S] [$p > 0.05$].

Discussion

The prognostic value of the Apgar score for detection of hypoxic ischemic brain disease is insufficient during the first hour, because it can be decreased during depression from maternal drugs, trauma, metabolic or infectious insults. Thus, a biochemical parameter that correlates with HIE is of interest [10]. Different kinds of markers have been studied to identify perinatal hypoxia, including electronic fetal heart rate monitoring, cord pH, electroencephalograms, and Doppler flow studies [3]. It is well known that birth asphyxia in newborn infants may cause hepatic hypoxic injury [10]. Various quantitative and qualitative changes occur in the liver after delivery. The activity of liver enzymes is low after birth. The changes of enzyme values [AST, ALT] depend on the course of pregnancy, and on the degree and intensity of asphyxia [11]. An increase in liver enzymes after birth asphyxia is well known and frequently seen in NICU [10]. However, few previous studies have addressed the temporal pattern of hepatic enzymes in clinical neonatal asphyxia [10]. The serum activity of AST and ALT is one of the more specific parameters of liver cell injury both in adults and pediatric age group [12, 13]. To know whether hepatic dysfunction can be employed as a prognostic tool for assessment of the level of hypoxia ischemic brain disease during the beginning hours of life, the study was undertaken.

There was a highly significant increase in the frequency of asphyxia in our study among those born by CS when compared to those with normal vaginal delivery. Also, a highly significant lower Apgar scores were detected among cases when compared to controls. These results are in accordance with Godambe et al., 1997, who reported that severe asphyxia was noted in 31% of normally delivered babies and in 64% of those delivered by CS or assisted deliveries. He explained this difference that most of his CS cases were urgent not elective [14]. But, Littleford, 2004, reported that even in elective CS, all medications administered to the mother cross the 098y877888placenta and enter the umbilical vein if given enough time, and a long incision to delivery time is associated with an increased incidence of fetal acidosis caused by uteroplacental vasoconstriction. Also, the inhalation agents used during anaesthesia, Desflurane, sevoflurane and high-dose non-depolarizing neuromuscular blockade [pancuronium, and atracurium] would be expected to cross the placenta and equilibrate in fetal tissues more rapidly resulting in a more depressed neonate [15].

Mueller et al. [1997] concluded that fetal acidemia was significantly increased after spinal anesthesia due to maternal arterial hypotension [16].

Littleford [2004] reported that the process of normal labour without anesthetic intervention, stresses the fetus so that mild acidosis develops in almost all labours. He also suggested that epidural anesthesia is associated with improvement in base excess, suggesting that placental exchange is well preserved in association with this technique [17].

ALT and AST levels increase as a result of hypoxia organ damage and mainly liver parenchyma, which calls for an equal amount of oxygen, glucose, and nutrients for use. Increased activities of ALT and AST are sensitive markers of impaired liver membrane. This study showed that the highest increase in ALT, AST and LDH in relation to baseline was observed after 3 days of delivery which then decreased below the baseline level after 6-12 days. Serum ALT elevation exceeding control values by +2SD was seen in 42 cases [70%] of the sixty asphyxiated infants. In 36 out of 60 cases [60%], the time course was compatible with hypoxic hepatitis, with a peak value at 3rd day then decreased below the baseline level after 6-12 days. AST and LDH followed a similar pattern to that of ALT. This was in agreement with Karlsson et al., 2006 [10]. He stated that AST and LDH had early peak at less than 12 hours after birth and late peak more than 24 hours after birth. He explained the two peaks of variation by the fact that most of cases with early peak had obstetric history of antepartum asphyxtic events and those with late peak had obstetric history of intrapartum asphyctic events.

Similarly, another study in Dhaka, Bangladesh on 70 full-term asphyxiated newborns; showed that serum AST, ALT and ALP increased more than the reference group and the differences were statistically significant [p 0.001]. Among the asphyxiated newborns 52.9% showed rise in AST, 87.1% showed rise in ALT and 32.9% showed rise in ALP.

Hepatic dysfunction based on raised amino transferases was present in 75-85% of the asphyxiated babies in different studies. The rise in Transaminases indicative of liver cell dysfunction is either due to hepatocyte necrosis or due to changes in cell permeability [14].

In the present study, AST, ALT, LDH all returned to normal levels after 6-12 days. Also Brucknerova et al, [2005] reported that there was a significant difference between AST values measured on the 1st and 5th day of life. A statistically important depression was found on 5th day of life in both preterm and full term asphyxiated newborns. In case of ALT, the same difference was found [11]. Goldberg et al. showed ALT ranged from 446-3050 IU/L in asphyxiated babies [13,17].

In ischemic or toxic liver injury, AST levels usually peak before those of ALT because of the enzyme's peculiar intralobular distribution [18]. Zone 3 of the hepatic acinus has a higher concentration of amino transferases, and damage to this zone, whether ischemic or toxic, may result in greater alteration to amino transferases levels. Amino transferase clearance is carried out within the liver by sinusoidal cells. Also, the half life in the circulation for ALT is about 47 hours and about 17 hours for AST and on average, 87 hours for mitochondrial AST [19].

It was reported that the diagnostic criteria for ischemic hepatitis include markedly elevated liver enzymes in the absence of a viral infection or chemical toxins, followed by a return to normal levels over a period of several days to a week [20].

In this study, most of asphyxiated cases suffered from intrapartum asphyctic events [n=32/60, 53%]. Decreased fetal movements during last 24 hours before delivery was reported in 20 cases [33%], abnormal fetal heart pattern in 16 cases [26%], abruption placenta in 12 cases [20%] and prolonged labour [n=6; 10%]. In the other 28 asphyxiated cases obstetric history was inconclusive.

It is reasonable to speculate that the hepatic effects of acute hypoxia-ischemia might be less severe in neonates because of the relatively hypoxemic blood supply of the liver during the antenatal period [21]. Moreover, serum Lactate Dehydrogenase [LDH] measured at 72 hours of age is the best choice to differentiate between asphyxia from a non-asphyxial etiology of non-specific clinical signs of illness in a newborn [22].

This study showed a significant increase in GGT above the baseline observed at 25-48 hours, while a non-significant increase in GGT at 49-72 hours. This is in accordance with Karlsson et al., 2006 [10] where samples were collected three times during the first 72 hrs and once between days 6 and 12 after birth. On the other hand, Diehl-Jones and Askin [2003] stated that hypoxic ischemic events in the perinatal period that result in hypoperfusion of the gut may be followed in one to two weeks by jaundice [23].

Also the study showed a highly significant positive correlation between each of ALT, AST and LDH versus the HIE stage. This was supported by Karlsson et al, [2006] who reported that a significant correlation between amino transferases values and the grade of HIE was found [10].

There was a significant increase in total and direct bilirubin after second and third day in comparison to baseline levels in our study. This is in accordance with Birrer et al., 2007 [1] who stated that bilirubin is mildly elevated in asphyxiated cases. Aslan et al, [2007] stated that bilirubin levels were higher in patients with severe and moderate hypoxemia compared to mild hypoxemia patients [24]. One study noted, TSB concentration ranged from 1.1-14.3 mg/dl and in another study, peak levels of total bilirubin ranged from 170-220umol/L.

In our study, in cases treated with anticonvulsant drugs [n=28; 47% of cases], there was no increase in serum bilirubin. Similar results were reported by Karlsson et al. [2006] who explained this by bilirubin conjugating enzymes induced by anticonvulsant drugs e.g. phenobarbitone [10].

The liver is the major site of synthesis of blood coagulation proteins. Abnormalities of coagulation results when there is impairment in ability of liver to synthesize these factors. Thus, it is a measure of liver dysfunction. There was a significant initial rise in INR on day 1 then a significant and a highly significant decrease on 3rd day and 6th-12th day respectively in comparison to the baseline level in our results. This was in agreement with results of Seeto et al. in 2000 [19]. Godambe et al. have shown that Prothrombin Index [PI] was reduced in all grades of asphyxia [14]. Another study showed that INR [International normalized Ratio] increased during the first 2 days of life in the asphyxiated group.

Hemoglobin level gradually decreased up to 72 hours follow up then started to increase again after 72 hours follow up. Our results are in accordance with that of Karlsson et al. [2006] who explained this by dilution with parenteral fluids or may be physiological anemia [10]. Bracci et al. [2002] found similar results and explained this low hemoglobin level by oxidative injury of red cells by severe hypoxia and acidosis which lead to increased hemolysis in the fetus as well as the newborn [25].

ALT was significantly higher among newborns with history of positive MAF in comparison to negative cases. This finding was not

previously reported by other studies, to the best of our knowledge. Martinez-Burnes et al. in 2001 stated that in cases with meconium aspiration, meconium acts as a toxic substance inducing injury of respiratory cells and inflammatory response characterized by release of cytosolic enzymes and neutrophil recruitment causing vigorous but transient leucocytic inflammatory reaction in the lung [26].

Hermansen [2003] and Leuthner and Das [2004] suggested there is an acidosis paradox, or a beneficial effect of a mild to moderate acidosis. One of the possible beneficial effects is that hypercarbia may result in cerebral vasodilation and increased cerebral blood flow. Second, acidosis has been shown to decrease cerebral metabolism and lower the oxidative needs of the brain. Finally, acidosis promotes the unloading of oxygen from fetal hemoglobin by shifting the oxygen dissociation curve. All three mechanisms lead to an adequate amount of oxygen delivery to the brain tissue, which potentially limits damage. These protective effects would be lost, however, with severe acidosis, which can lead to decreased cardiac output and cerebral ischemia [27,28].

In the study by Tariqul Islam, 2010 in Bangladesh, correlation between different stages of HIE with different parameters of liver function tests in the study group showed that serum AST, ALT, ALP, and PT levels were significantly positively correlated with different stages of HIE. However, TSB, STP and serum albumin showed negative correlation with different stages of HIE and not statistically significant [13].

Conclusion

We concluded that estimation of hepatic enzymes (ALT, AST, LDH) at early hours of life can be useful as a diagnostic tool to differentiate between asphyxiated neonates from non-asphyxiated neonates as well as to detect the severity of parental asphyxia and thus early treatment can be provided on the basis of liver function tests.

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