Early Predictors of Neonatal Hypoxic Ischemic Encephalopathy

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ABSTRACT

Background: Perinatal asphyxia is a major cause of neurologic morbidity and mortality in infants. Early assessment of the severity of an acute cerebral lesion secondary to hypoxia-ischemia may provide a very useful basis for prevention or therapeutic decision in affected neonates.

Aim: To determine the predictive value of serum level of amyloid A protein, lactate dehydrogenase and IL-6 and the occurrence of neonatal hypoxic ischemic encephalopathy (HIE) and its severity

Methods: Serum amyloid A protein, lactate dehydrogenase and IL-6 were measured in the blood samples which were collected from 27 cases with evidence of perinatal asphyxia and 25 healthy controls within the first 12 hours after birth.

Results: Serum amyloid A, lactate dehydrogenase and IL-6 were significantly increased in HIE cases in comparison to controls(p<0.001), moreover their levels were significantly correlated with the severity of hypoxic ischemic encephalopathy (161.0±13.4 vs 87.5±6.7 vs 67.1±15.8) for amyloid A, (4040±513 vs 2266.5±314.6 vs 961.4±162.9) for lactate dehydrogenase and (259.3±9.4 vs 153.2±12.0 vs 81.5±11.7) for IL-6 in mild, moderate and severe hypoxic ischemic encephalopathy respectively(p<0.001).

Conclusion: Serum amyloid A protein, lactate dehydrogenase and IL-6 levels were increased in hypoxic neonate and their levels were correlated with the severity of neonatal hypoxic ischemic encephalopathy. So, the assessment of their levels may be useful to identify early, and in a relatively simple way, those who are most likely to have subsequent brain injury and adverse outcome.

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Introduction

Asphyxia neonatorum before, during and after birth is one of the most important factors contributing to neonatal morbidity and mortality worldwide. The clinical signs following asphyxia neonatorum, traditionally called hypoxic ischemic encephalopathy, has a grading of mild, moderate and severe which in some cases may lead to neurological sequelae including mental retardation, cerebral palsy and epilepsy (1,2,3). While, in most cases, the clinical symptoms and signs of moderate and severe hypoxic ischemic encephalopathy are obvious, the neonatal symptoms and signs of mild hypoxic ischemic encephalopathy are more subtle making an early precise diagnosis more difficult. Early prediction of hypoxic ischemic encephalopathy is needed for selection of newborn infants who could benefit from neuroprotective treatment like hypothermia (4,5).

After hypoxic-ischemic insults, there may be secondary brain injury through the production of proinflammatory cytokines (IL-1β, IL-6 & TNF-α). (6,7,8)

Serum amyloid A (SAA) is an apolipoprotein that is found in the high-density lipoprotein fraction of serum and is involved in the chemotactic recruitment of inflammatory cells to the site of inflammation(9) and its expression is largely triggered by increased circulatory concentrations of proinflammatory cytokines, which may be used as markers for neonatal hypoxic ischemic encephalopathy(10). Amyloid A protein is considered a specific marker for ischemia-related inflammation, the condition that exactly pertains to hypoxic ischemic encephalopathy, also it has a role in the pathogenesis of inflammation and its reduction can potentially be helpful in the treatment of ischemic disease and its level correlates accurately not only with acute inflammation but also with intensity and degree of tissue damage and with cell necrosis (11,12,13).

In hypoxic ischemic encephalopathy the injured cells leak intra-cellular enzymes, some of which are easy to measure in plasma e.g. lactate dehydrogenase (LDH), the increased level of that enzyme has been reported after...
neonatal asphyxia, and this make this enzyme can be used as a predictor of neonatal hypoxic ischemic encephalopathy as it rise after cell damage following asphyxia and also can be used to detect the severity of hypoxic ischemic encephalopathy insult in the period (14,15).

Patient & Method

This study was conducted in Tanta University hospital on 27 cases with evidence of perinatal asphyxia (group I) and 25 healthy controls (group II).

Perinatal asphyxia was diagnosed by the presence of at least three of the following criteria: (1) apgar score ≤ 5 at 10 min after birth or, (2) umbilical arterial PH (PHa) < 7 or base deficit ≥ 16 mmol / l or (3) resusitation with more than 10 min of positive pressure ventilation before stable spontaneous respiration. Encephalopathy was graded as mild, moderate and severe using the Sarnat system (7).

Blood samples were collected from cases and controls during the first 12 hours after birth. Serum was separated by centrifugation and stored at -20 °C. Serum levels of AA & IL-6 were determined by commercial enzyme-linked immunosorbent assay (ELISA) kit (R&D System, Inc. MN, USA) according to the manufactures instructions, serum level of LDH was determined using Clinical Chemistry Kits (BQKITS Diagnostics, USA).

Data are expressed as mean (SD). Statistical analysis was done using STSS software version 17 for windows. Using ANOVA and Chi-square; analysis was performed to compare between the different groups with P < 0.05 was statistically significant.

Results

Neonates included in this study were classified into two groups; group (I) which include 27 HIE cases and group (II) which include 25 controls. The demographic and laboratory findings of the study population were presented in table (1). There was a significant difference in the serum levels of IL-6, SAA and LDH between the two studied groups with P value 0.001 for each.

Table 1: The demographic and laboratory findings of all studied neonates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
<th>Controls</th>
<th>T-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.A</td>
<td>34.0 - 40.0</td>
<td>33.0 - 40.0</td>
<td>1.737</td>
<td>0.0885</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2.0 - 4.1</td>
<td>2.3 - 4.0</td>
<td>0.223</td>
<td>0.824</td>
</tr>
<tr>
<td>IL-6 (pg / ml)</td>
<td>64.5 - 272.0</td>
<td>125.4 ± 66.4</td>
<td>9.079</td>
<td>0.001*</td>
</tr>
<tr>
<td>SAA (μg/ml)</td>
<td>30.9 - 175.0</td>
<td>86.2 ± 36.2</td>
<td>11.128</td>
<td>0.001*</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>775.0 - 4490.0</td>
<td>1736.2 ± 1169.9</td>
<td>5.245</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* P < 0.05 significant

As regard the correlation between the levels of the estimated markers and the severity of HIE, Table (2) illustrated an upward trend in their values with the increasing severity of HIE. It was seen and this was statistically significant, (161.0±13.4 vs 87.5±6.7 vs 67.1±15.8) for amyloid A, (4040±513 vs 2266.5±314.6 vs 961.4±162.9) for lactate dehydrogenase and (259.3±9.4 vs 153.2 ± 12.0 vs 81.5±11.7) for IL-6 in severe, moderate and mild hypoxic ischemic encephalopathy respectively (p=0.001). Figures [1(a,b&c)].

Table 2: Levels of SAA, IL-10 and LDH in cases of neonatal HIE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>Mild</td>
<td>64.5 - 100.1</td>
<td>81.5 ± 11.7</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>139.0 - 172.0</td>
<td>153.2 ± 12.0</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>250.0 - 272.0</td>
<td>259.3 ± 9.4</td>
</tr>
<tr>
<td>SAA</td>
<td>Mild</td>
<td>30.9 - 95.0</td>
<td>67.1 ± 15.8</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>78.0 - 95.0</td>
<td>87.5 ± 6.7</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>149.0 - 175.0</td>
<td>161.0 ± 13.4</td>
</tr>
<tr>
<td>LDH</td>
<td>Mild</td>
<td>775.0 - 1301.0</td>
<td>961.4 ± 164.9</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1960.0 - 2601.0</td>
<td>2266.5 ± 314.6</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3591.0 - 4490.0</td>
<td>4040.0 ± 513.9</td>
</tr>
</tbody>
</table>
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* P < 0.05 significant

Figure 1: Levels of SAA, IL-10 and LDH in cases of neonatal HIE

The results of this study revealed that there was a positive significant correlations between the different markers in the studied groups as shown in table (3), figure[2(a,b&c)]

Table 3: The correlation between the IL-6, SAA & LDH

<table>
<thead>
<tr>
<th></th>
<th>IL-6</th>
<th>SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAA</td>
<td>r</td>
<td>0.882</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDH</td>
<td>r</td>
<td>0.972</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* P < 0.05 significant

Figure 2: The correlation between the IL-6, SAA & LDH

Discussion

Many physiopathological mechanisms involved in the brain damage related to hypoxic-ischemic encephalopathy 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 decisions in affected neonates (18).

A number of parameters have been studied in the aim to provide an early and reliable marker of tissue injury for diagnostic and prognostic purpose. Some authors have even suggested that biochemical indicators may be more effective than the results of clinical, Apgar score, pH in cord blood, electroencephalographic and neuroimaging data.(19)
Hypoxia ischemia of the newborn can trigger an acute phase inflammatory response which involves the expression of different acute phase reactant mediators including serum amyloid A (20). The serum amyloid A is not only a reactant to initial inflammation but also reflect the degree of cell death (21).

The results of this study detected that SAA values were raised significantly in HIE as compared to non hypoxic group, and its level were correlated with the severity of HIE. This agreed with the study which stated that the increased serum amyloid A in asphyxia is a true marker for the amount of tissue damage and cell death and it also represent the acute inflammatory response that follows hypoxia ischemia (22). Liu et al (2004) (23), also detected that SAA was significantly increased in neonates with HIE than normal neonates and related with the prognosis of HIE, moreover they concluded that determining SAA was important in early phase diagnosis and evaluate the degree of cell death.

The same results were found by Aly et al (2010) (24) as they reported that SAA concentrations were significantly related with the severity of HIE (146±56.4 vs 79.8±24.7 vs 58.1±21.5 ) in sever, moderate and mild HIE respectively (p<0.001).

Our results showed that serum LDH were significantly related with the occurrence and the severity of HIE, these results are in agreement with the results done by some authors (25) who reported that serum levels of LDH enzyme concentration are higher in asphyxiated neonates than in normal neonates. These elevations seemed directly to be depend on a diminished oxygen supply of the fetus during prenatal, natal and postnatal period(26). In neonates, serum concentration of LDH was significantly higher in neonates with HIE than in normal neonates with good sensitivity and specificity, and acceptable positive and negative predictive values(26).

The plasma level of lactate dehydrogenase enzyme predicted neonatal hypoxic ischemic encephalopathy with high sensitivity and specificity and also correlated with the severity of hypoxia as mild, moderate, severe neonatal hypoxic ischemic encephalopathy, the LDH also showed a good predictive value before the onset of seizures, so that the LDH enzyme is used for early identification of candidates for hypothermia treatment (27).

LDH levels correlate to nucleated red blood cells during late fetal life, a known indicator of chronic hypoxia and the LDH is present in all tissue as a marker of cell damage and injury and adverse outcome and who could benefit from neuroprotective strategies.

On the other hand, Karlsson et al (2010) (29) found that the LDH was significantly higher (p<0.0001) in the HIE group compared with the non- HIE group.

LDH values were raised significantly in asphyxiated newborn and the increase is more marked among those who developed HIE, moreover its values raised with the increasing severity of HIE but this was not statistically significant(30). This differences with our results could be explained by the difference in the time point for blood collection.

In the present study IL-6 were significantly increased in HIE group in relation to control group and its values in HIE cases were significantly correlated with the severity of the cases. In agreement with our results, some results detected that serum IL-6 concentrations in the infants who developed HIE were significantly elevated than normal infants, moreover(31,32) found that serum IL-6 concentrations in the HIE infants 43 folds higher compared to values in the normal infants (p<0.001) and its concentrations were also related to the severity of HIE(33), while some authors(34) found that the cord IL-6 concentrations in the infants who developed HIE was 376 fold as high as the values in the normal infants (p< 0.0001) and 5.5 fold as high as those in infants with asphyxia who did not develop HIE (p<0.05). There was also a significant relation between IL-6 and the degree of HIE (35,36).

Aly et al (2006) (37) observed in 24 term infants with HIE that the neurological outcomes at 6 months of age correlated significantly with the levels of IL-1β and IL-6. Infants who died had higher concentration of IL-6 compared to those who survived.

Some studies found that during the first 4 h of hypoxic insult, there is liberation of interleukin-6 (IL-6) (37) who have reported statistically significant increases in concentrations of IL-6 in asphyxiated neonates, and a close correlation between these concentrations and degree of HIE. These findings suggested that IL-6 level might be a good indicator of the severity of encephalopathy (37,38).

Conclusion

Serum amyloid A protein, lactate dehydrogenase and IL-6 levels were increased in hypoxic neonate and their levels were correlated with the severity of neonatal hypoxic ischemic encephalopathy. So, their levels may be good predictors to identify early, and in a relatively simple way, those who are most likely to have subsequent brain injury and adverse outcome and who could benefit from neuroprotective strategies.

References


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