Cord blood IGF-1 and IGFBP-3 levels in asphyxiated term newborns

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Abstract

OBJECTIVE: Determination and pathogenesis of perinatal asphyxia is still an important problem. During the asphyxial insult and recovery phase, alteration of the growth factors has been demonstrated and there is evidence that expression of insulin-like growth factors (IGF) and their insulin-like growth factor binding proteins (IGFBP) in injured sites in experimental studies. Aim of this study was to evaluate relationship between serum IGF-1, IGFBP-3 levels and perinatal asphyxia.

PATIENTS AND METHODS: 18 term-newborn who defined as perinatal asphyxia and 12 term-healthy newborn were enrolled. Umbilical cord IGF-1 and IGFBP-3 levels were detected and searched correlation with apgar scores and umbilical artery gas analysis as pH, pCO₂, pO₂, base excess, HCO₃, ctO₂, SO₂ and lactate levels.

RESULTS: Cord blood IGF-1 and IGFBP-3 levels for asphyxiated newborns were lower than normal group (27.8±2.6 ng/ml, 55.1±2.8 ng/ml respectively, p<0.01 for IGF-1; 1 107.7±320.4, 1 682.5±364.1, p<0.001 for IGFBP-3). Cord blood IGF-1 levels were positively correlated with birth weight; first and 5th minute Apgar score, cord blood arterial pH, ABE, HCO₃, SO₂ levels. Cord blood IGFBP-3 levels were positively correlated with first and 5th minutes Apgar scores, cord blood arterial pH, pCO₂, ABE, HCO₃, SO₂, and also negatively correlated with cord CO₂ and cord lactate levels.

CONCLUSIONS: Our study demonstrates that exposure to hypoxia and acidosis at birth strongly correlated with a fall in IGF-1 and IGFBP-3 levels in cord blood.

Introduction

Perinatal asphyxia continues to be a major cause of neonatal deaths and neurodevelopmental sequel despite marked improvement in perinatal care. Asphyxial insult, which in majority occurs in utero or intrapartum period, can trigger a cascade of pathophysiological events. While multiple biochemical cascades contribute to the pathogenesis of hypoxic-ischemic brain injury, at the same time protective mechanisms operate to prevent from ongoing injury [1–2]. During the asphyxial insult and recovery phase, alteration of the growth factors has been demonstrated and there is evidence that expression of insulin-like growth factors (IGF) and their insulin-like growth factor binding proteins (IGFBP) in injured tissues reduce cell death and improve tissue repair [3–6]. Animal studies suggest that circulating IGF-1 concentrations are influenced by hypoxia [7–8].
Since acid-base analysis of umbilical artery cord blood is a reliable indicator of fetal oxygenation in utero and at birth, we determined the relationship between umbilical cord IGF-1 and IGFBP-3 levels and umbilical cord blood gases and lactate levels. We tried to investigate the impact of asphyxia on the umbilical cord blood levels of IGF and IGFBP-3.

Materials and methods

The study group consisted of 18 newborn with perinatal asphyxia and 12 healthy gestational age and weight matched newborn. Because birth weight and gestational age could influence the serum levels of IGF-1 and IGFBP-3, all infants included to this study were term (gestational age>37 weeks) and appropriate for gestational age (birth weight is between 2 500–3 600 g). Clinical data of newborns, including gestational age, sex, birth weight, maternal age, were collected at the time of the study from each case. Gestational age was determined by New Ballard scoring system. Umbilical cord arterial blood (2 ml) was drawn at birth from each case, to assess pH, pCO₂, pO₂, HCO₃, ABE, SO₂, ctO₂, and lactate levels. Perinatal asphyxia was determined on the basis of a cord blood pH<7.1 and 5 minute Apgar score <6. First, 5th and 10th minutes Apgar scores were also recorded. After clamping the umbilical cord, umbilical artery and umbilical vein samples and 5 ml serum samples for IGF study were obtained. Cord blood sample were immediately centrifuged and serum aliquots frozen at –70 °C until subsequent analysis. Serum IGF-1 and serum IGFBP-3 levels were measured in samples of serum using a two-sided immunoradiometric assay (non-extraction test, IBL-Immunobiological Laboratories, Hamburg, Germany).

Table 1. Mother's age, birth weight, umbilical artery parameters and umbilical cord IGF-1 and IGFBP-3 levels of study group.

<table>
<thead>
<tr>
<th></th>
<th>Asphyxia group (n=18)</th>
<th>Controls (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's age (year)</td>
<td>29.8 ± 1.2</td>
<td>28.0 ± 1.6</td>
<td>ns</td>
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<tr>
<td>1st minute Apgar score</td>
<td>3.22 ± 0.54</td>
<td>9.16 ± 0.16</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>5th minute Apgar score</td>
<td>5.83 ± 0.47</td>
<td>9.91 ± 0.08</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3 144.4 ± 81.1</td>
<td>3 400.0 ± 110.2</td>
<td>ns</td>
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<tr>
<td>Umbilical artery pH</td>
<td>7.06 ± 0.02</td>
<td>7.34 ± 0.02</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>pO₂</td>
<td>15.2 ± 0.9</td>
<td>22.0 ± 2.0</td>
<td>p&lt;0.001</td>
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<tr>
<td>pCO₂</td>
<td>66.2 ± 3.3</td>
<td>38.1 ± 2.7</td>
<td>p&lt;0.001</td>
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<tr>
<td>ABE</td>
<td>–15.5 ± 0.7</td>
<td>–3.9 ± 1.1</td>
<td>p&lt;0.0001</td>
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<tr>
<td>HCO₃</td>
<td>12.3 ± 0.5</td>
<td>19.4 ± 0.5</td>
<td>p&lt;0.001</td>
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<tr>
<td>SO₂</td>
<td>18.7 ± 1.4</td>
<td>53.7 ± 4.2</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>ctO₂</td>
<td>4.32 ± 0.3</td>
<td>12.2 ± 1.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Lactate</td>
<td>66.7 ± 4.6</td>
<td>22.0 ± 3.3</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>IGF-1</td>
<td>27.8 ± 2.6</td>
<td>55.1 ± 2.8</td>
<td>p&lt;0.01</td>
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<tr>
<td>IGFBP-3</td>
<td>1 107.7 ± 320.4</td>
<td>1 682.5 ± 364.1</td>
<td>p&lt;0.001</td>
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</table>

All parameters were showed as standard ± standard error mean, except IGF-1 and IGFBP-3 as median

Statistical analysis was studied with SPSS for Windows 10.0. Although umbilical cord IGF-1 and IGFBP-3 levels were not normally distributed, Mann-Whitney U test was used for comparison and logarithmic transformation performed for correlation analysis. Relationships between logIGF-1 and logIGFBP-3 levels with cord blood gas analysis parameters were evaluated with Pearson correlation analysis. The statistical significance was taken as p<0.05.

Results

Means of maternal age, birth weight, APGAR scores, blood gas parameters and cord blood IGF-1 and IGFBP-3 were given in Table 1 for both groups. Cord blood IGF-1 levels for asphyxiated newborns were lower than normal group (27.8±2.6 ng/ml, 55.1±2.8 ng/ml respectively, p<0.01). Cord blood IGFBP-3 levels also lower in asphyxia group (1 107.7±320.4, 1 682.5±364.1, p<0.001).

Cord blood IGF-1 levels were positively correlated with birth weight, first and 5th minute Apgar score, cord blood arterial pH, ABE, HCO₃, SO₂, ctO₂, and lactate levels (r=0.453, p<0.05; r=0.554, p<0.01; r=0.539, p<0.01; r=0.452, p<0.05; r=0.467, p<0.05; HCO₃ r=0.594, p<0.01, r=0.416, p<0.05). Cord blood IGFBP-3 levels were positively correlated with first and 5th minutes Apgar scores, cord blood arterial pH, pCO₂, ABE, HCO₃, SO₂, ctO₂ and lactate levels (r=–0.698, p<0.001; r=–0.790, p<0.001; r=–0.685, p<0.001; r=–0.700, p<0.001; r=–0.742, p<0.001; r=–0.638, p<0.01; r=–0.661, p<0.001). Cord blood IGFBP-3 levels were also negatively correlated with cord CO₂ and lactate levels (r=–0.478, p<0.05; r=–0.533, p<0.01).
Discussion

In our study we selected only term AGA infants to exclude the physiological changes due to maturation, in IGF-1 and IGFBP-3 levels and also to exclude the effect of chronic asphyxia which cause intrauterine growth restriction. By this way we explore acute changes in the serum levels of IGF-1 and IGFBP-3 in asphyxiated newborns with hypoxia. In our study IGF-1 level in the study group was lower than the control group and decreased IGF-1 levels in cord blood was positively correlated with pH, base excess and first and 5th minute Apgar score. Cooley et al. [9] reported that those fetal cord IGF-1 levels were correlated with fetal acidosis at birth. Several experimental studies have demonstrated that during moderate acute and prolonged hypoxia, there is a small acute fall in circulating IGF-1 levels [10–11]. Bennet et al. [8] determined IGFs and IGFBPs in premature fetal sheep before and after asphyxia by cord occlusion. During the acute phase of recovery from asphyxia there was a profound fall (80%) in circulating levels of IGF-1. Kornhauser et al. [12] concluded that serum IGF-1 is lower in asphyxiated newborns, perhaps a result of hypoxia. The significance of the post-asphyxial fall in IGF-1 is unknown. It has been speculated that the low plasma levels of IGF-1 following trauma or hypoxic-ischemic injury could reflect redistribution or targeting of IGF-1 from the peripheral blood plasma pool to injured tissue [13–15]. Gluckman et al. [5] showed that IGF system activated by hypoxic-ischemic injury with IGF-1, IGFBP-2 and IGFBP-3 being induced in glial cells in the region of injury, in initial few days.

In our asphyxiated cases, cord blood IGFBP-3 levels were also lower than the control group and were positively correlated with first and 5th minutes Apgar scores, cord blood arterial pH, ABE, HCO₃, SO₂, ctO₂ and negatively correlated with pCO₂ and lactate levels. Since IGFBP-3 is the main carrier protein for IGF-1, we can speculate that reduced levels of IGFBP-3 in cord blood is due to the migration of IGFBP-3 bounded with IGF-1 to injury site.

Accordingly, it is not surprising that such growth factors would be altered by cerebral hypoxia-ischemia, and that their administration might be neuroprotective. Since central administration of IGF-1 after cerebral ischemia in fetal sheep or hypoxia-ischemia in adult rats can reduce both infarction and selective neuronal loss in a dose-dependent manner [4], Gluckman et al. [5] have found a concomitant reduction in the incidence of post-asphyxial seizures and secondary cytotoxic edema. Perhaps administration of IGFBP-3 together with IGF-1 will be helpful for the action of IGF-1 in the injured site.

Early detection of the degree of cerebral damage in newborns who suffered birth asphyxia is relevant to prognosis and treatment strategies. Defining the alteration of these growth factors in response to asphyxia may contribute to explain the pathogenesis and neuroprotective mechanisms in the evidence of perinatal asphyxia. This study shows that IGF-1 and IGFBP-3 are well correlated with umbilical cord blood gases and lactate levels. Since the degree of asphyxia affects the degree of neuronal damage, treatment strategies with growth factors to prevent further neuronal damage, can be planned on the basis of cord blood IGF-1 and IGFBP-3 levels.

REFERENCES