Cerebral Disorders of Preterm Infants from Women with Autoimmune Disorders of Pregnancy

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Abstract

Introduction. The objective of study was to determine the severity of central nervous system (CNS) injury and main perinatal outcome of infants born to women with antiphospholipid syndrome.

Material and methods. 100 women with abnormal pregnancy and intrauterine chronic hypoxia were examined. In 30 of the women positive level of anticardiolipin antibodies (ACA) was found. 70 preterm babies from mothers with negative titer of anticardiolipin antibodies, but exposed to intrauterine hypoxia were investigated as control study. Brain tissue damage was estimated on the base of neurospesific enolase (NSE) and glial fibrillary acid protein (GFAP) levels in umbilical cord blood (UCB) and in the peripheral blood during early neonatal period. Level of both neurospesific proteins were detected by immunoenzyme assay.

Results. NSE level was higher in very low birth weight (VLBW) infants of both subgroups. GFAP level in UCB of all infants from ACA positive mothers was higher and more significantly difference (p<0.05) detected between VLBW babies from ACA positive women and control babies. To the end of early neonatal period GFAP of VLBW newborns of this group was statisically increased till 66,8±3,2. But NSE level stayed as high as in the first hours of life.

Conclusion. High level of GFAP till the end of neonatal period of these babies confirms continuing of ischemic process and severe perinatal ensephalopathy.

Key words: hypoxic, encephalopathy, antiphospholipid, neurospesific, enolase, brain injury

1. Introduction.

The hypoxic-ischemic encephalopathy is one of the actual problems of perinatal period resulting in high percent of morbidity and main cause of severe neurologic deficits in children (1,2). Despite improvements in perinatal technologies, the severity and incidence of cerebral disorders have not changed.
So during last several decades management strategies in perinatal pathologies targeted towards the patophysiology of ongoing injury. Moreover, previous commonly used single markers have been replaced in more sensitive and specific markers for accurate diagnosis and prognosis of perinatal encephalopathy (3,4). Our hypothesis was that combination of perinatal risk factors, such as intrauterine hypoxia and autoimmune lesion of neuronal system may result in more serious perinatal complications. The objective of study was to determine the severity of central nervous system (CNS) injury and main perinatal outcome of infants born to women with antiphospholipid syndrome.

2. Material and methods.

The study was approved at the Neonatology department of Azerbaijan Medical University and at the Baku Maternity Hospital after name Sh.Alasgarova. 100 women with abnormal pregnancy and intrauterine chronic hypoxia were examined. The main causes of pregnancy complications were nephropathy of pregnancy and anemia. Intrauterine hypoxia was estimated by Doppler examination of uteroplacental circulation and cardiotocography of fetus. In 30 of the women positive level of anticardiolipin antibodies (ACA) was found, which in 25 of ACA positive women it was detected antiphospholipid syndrome (APS). APS was diagnosed in pregnant women by anamnesis, clinic symptoms and laboratory tests (thrombocytopenia, positive level of anticardiolipin antibodies and lupus test) on the base of International consensus statement of the classification criteria for this pathology (5). 30 preterm infants from women with positive ACA were categorized as 20 low birthweight (LBW) and 10 very low birthweight (VLBW) newborns. 70 preterm babies from mothers with negative titer of anticardiolipin antibodies, but exposed to intrauterine hypoxia were investigated as control study and for adequate comparison they were categorized as LBW (n=40) and VLBW (n=30) subgroups too. In addition to clinical, ultrasound examinations, brain tissue damage was estimated on the base of neurospecifc enolase (NSE) and glial fibrillary acid protein (GFAP) levels in umbilical cord blood (UCB) and in the peripheral blood (PB) during early neonatal period. Level of both neurospecifc proteins were detected by immunenzyme assay.

Non-parametrical Wilcoxon rank sum test and t-Test was used for univariate analysis. Categorical or nominal variables were compared using Fisher's exact test. A P-value of <0.05 was decided arbitrarily for statistical significance.

3. Results

Anticardiolipin antibodies in UCB detected significantly higher (p<0.001), approximately twice more in VLBW infants (76,5±2,6 GPL) than in LBW babies (39,6±2,1 GPL). Hence, it was also defined positive correlation between the levels of both neurospecifc proteins and the titer of anticardiolipin antibodies (p<0,05). So, high titer of ACA associated with in much more amount of appearance of neuronal tissue lesion markers in umbilical cord blood (Figure 1). The level of neurospecifc proteins in umbilical cord blood were as following: NSE level was higher in VLBW infants of both subgroups. GFAP level in UCB of all infants from ACA positive mothers was higher and more significantly difference (p<0.05) detected between VLBW babies from ACA positive women and control babies (table). To the end of early neonatal period GFAP of VLBW newborns was statisically increased till 66,8±3,2. But NSE level stayed as high as in the first hours of life.

As described in according literature, levels of both proteins increase in cerbrospinal liquid and peripheral blood during neuronal tissue damage (6). NSE is high from the first hour of life in all preterm babies from mothers with APS and stays stable during early neonatal period. As NSE is cytoplasm protein of dendritis, executes ferment functions, acts in glycolysis and is considered one of the most specific marker for neuronal injury, so it points in intrauterine neuronal damage of these infants (7). But GFAP level of VLBW infants increased and differs significantly to the end of early neonatal period of life. GFAP is cytoplasm protein forming microphilaments which form cytoskeleton of macroglia. It is found in good supply in subependim astrocytes of periventricular area and also in epiphysis, hypophysis and immature oligodendrogliacytes (8). Increased level of this protein points in continuing glial cells damage after birth in VLBW infants from mothers with APS. These changes were expressed in clinical and ultrasound results of studied babies (figure 2).

All VLBW infants from ACA positive women born in severe asphyxia and it was detected periventricular leucomalacia in half of children (50%), intracranial haemorrhage in 50% of case, brain tissue edema in 33% of case in ultrasound examination. In comparison with control infants, only 40% of VLBW babies born in severe asphyxia, periventricular leucomalasia occurred in VLBW infants and in 10% of case.
Hence, more than two days resuscitation have been performed to all infants born to mothers with APS. Only 40% of infants had been transported to NICU for further treatment and 60% of death occurred till the end of early neonatal period.

Thus, preterm delivery of women with positive level of antiphospholipid antibodies in pregnancy associate with severe brain injury of infants and VLBW infants include in higher risk group for acute and more serious neuronal damage.

High level of GFAP till the end of neonatal period of these babies confirms continuing of ischemic process and severity of perinatal encephalopathy.

4. Discussion.

However, it is not excluded, that exactly CNS defeat in antenatal period underlies many diseases and metabolic frustrations proving the next years of a life that gives the basis for carrying out of research works in this aspect. We are continuing next stage of this research in experiment for confirmation of available results and detection of further news. In addition to prenatal prophylaxis and neonatal care babies from mothers with APS must undergo long term control. Because the injury of periventricular space and other neurons manifests with obvious neurologic symptoms just from birth, continuing glial damage does not appear with obvious clinical and laboratory signs each time. From these positions studying the role of autoimmune antibodies in pathogenesis of hypoxic-ischemic encephalopathy matters not only for working out of methods of early preventive maintenance and treatment in neonatal period, but also creates opportunities for protection of health of an organism during further age periods.

Fig. 1. GFAP and NSE concentration depending on ACA antibodies level of umbilical cord blood

![Graph showing GFAP and NSE concentration](image)

Fig. 2. Cerebral disorders in early neonatal period of infants born to mothers with positive level of ACA

![Graph showing cerebral disorders](image)

Fig. 3. Main perinatal outcome of infants born to women with APS

![Graph showing main perinatal outcome](image)
Table. Level of neurospesific proteins in UCB and PB

<table>
<thead>
<tr>
<th>Neurospesific proteins</th>
<th>LBW</th>
<th>control LBW</th>
<th>p value</th>
<th>VLBW</th>
<th>control VLBW</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE in UCB (ng/ml)</td>
<td>19.5±1.6</td>
<td>18.6±1.3</td>
<td>0.98</td>
<td>46.5±2.1</td>
<td>32.8±1.6</td>
<td>0.06</td>
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<td>GFAP in UCB (ng/ml)</td>
<td>24.6±1.3</td>
<td>15.3±1.3</td>
<td>0.34</td>
<td>30.4±1.6</td>
<td>20.2±1.1</td>
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<tr>
<td>NSE in PB (ng/ml)</td>
<td>28.6±1.2</td>
<td>20.2±1.1</td>
<td>0.06</td>
<td>40.2±1.4</td>
<td>39.6±1.4</td>
<td>0.9</td>
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<tr>
<td>GFAP in PB (ng/ml)</td>
<td>30.2±1.4</td>
<td>25.6±1.3</td>
<td>0.08</td>
<td>66.8±1.3</td>
<td>28.2±1.1</td>
<td>0.001</td>
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</tbody>
</table>

References