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### Impaired Metabolism Induced By Perinatal Hypoxia

Zisovska Elizabeta\*1, Trajkova Kornelija<sup>2</sup>

Obstetric and Gynecology Clinic, Skopje, Macedonia

Abstract - Perinatal hypoxia induces disturbances in glucose metabolism. In anaerobic environment, high level of lactate production persists, causing endothelial damage and deleterious effect on the brain. The outcome depends on the brain capacity to utilize lactate and ketones as an alternative energy source to glucose. There isn't evidence that depriving infants of glucose after hypoxia is neuroprotective. The aim of our study was to present the results of blood investigation for blood sugar level (BSL), lactate level (LL), and to assess the correlation between these markers and severity of Hypoxic-ischemic encephalopathy (HIE). Material: asphyxiated newborns born at Obstetric&Gynecology Clinic in Macedonia. Methods: clinical, biochemical, statistical. Results: at first sight we got almost normal value of BSL (mean value in healthy full-term infants was 2,8 mmol/l, in examined group 2,7 mmol/l), but deep analysis of distribution showed three-modal curve: 33% of them had normal value (3,1 mmol/l), 43% of the babies were hypoglycemic (BSL 1,3 mmol/l) and 24% were hyperglycemic with BSL of 4,8 mmol/l. The LL had very concordant distribution: in hypoglycemic infants LL was much lower than normal values (<0,9 micromol/l compared to normal value 1,2-1,8 micromol/l), similar in normoglycemic infants (LL was 1,0 micromol/l), in hyperglycemic the LL increased significantly to 2,8 micromol/l,. The Spearman coefficient of correlation showed moderate level of correlation between LL and severity of HIE (r=0.65). Conclusion: perinatal hypoxia is still important cause of brain damage, and the management of hypoxic baby includes careful maintenance of glycaemia and other homeostatic parameters.

Keywords: newborn, hypoxia, blood sugar, lactates.

#### INTRODUCTION

Birth asphyxia takes a certain part in the neonatal morbidity and mortality, and in full-term infants is still an important cause of neurologic disability and long term handicap. 1 Secondary to birth asphyxia, a postnatal manifestation of hypoxic-ischemic encephalopathy (HIE) is frequently observed being associated with either mild or severe organ damage in asphyxiated newborns, both leading development of chronic pathologies. The severe insults often cause neurodegenerative diseases, mental retardation and epilepsies. The mild insults lead to socalled "minimal brain-damage disorders" such as attention deficits and hyperactivity, but can also be associated with the development of schizophrenia and life-long functional psychotic syndromes. In some particular cases it is difficult to discriminate between mild and severe asphyxia: advanced methodology to improved diagnosis of birth asphyxia and prediction of individual short- and long-term outcomes obligatory needs to be developed. The task of individual prediction, targeted prevention and personalized treatments before a manifestation of life-long chronic pathologies usually developed by asphyxiated

newborns, should be given the extraordinary priority in pediatrics<sup>2</sup>.

The pathogenesis of the consequent hypoxic-ischemic encephalopathy (HIE) is based on the sequence exposure-response-outcome, which is modulated by the time of exposure, and on the other hand by the vulnerability of the brain tissue. This insult causes a cascade of numerous biochemical events on the cellular level, which can lead to neuronal death. Many other disturbances occur in perinatal hypoxia, not only while experiencing the insult, but also suppression and over-activation of the affected molecular pathways occur during both periods: hypoxia and disturbances<sup>3</sup>. oxygenation, including vascular pulmonary damage, hepatic malfunction, and even tissue remodeling. 4

Hypoxic ischemic organ damage can occur at antepartum—prenatal asphyxia, at intrapartum—perinatal (birth) asphyxia, or after delivery as postpartum asphyxia. Acute maternal infections, prematurity of a newborn and multiple births are the most frequent natural risk factors leading to hypoxic conditions in a fetus or newborn.<sup>5</sup>

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The consequently triggered cascade of biochemical events creates a significant imbalance in central oxygen-dependent molecular pathways. Even more damaging is the reversion to normal oxygen levels during the post-asphyctic re-oxygenation associated with an extensive production of highly reactive oxygen species. Respectively, suppression and over-activation of the affected molecular pathways occur during both periods: hypoxia and re-oxygenation <sup>6,7</sup>.

In normal circumstances there is a cell's balance of the production and spending of high energetic molecules of Adenosine three phosphate. In mitochondria is going process of oxidative phosphorylation. In a condition of intracellular hypoxia, net catabolism of ATP results in deliberation of adenine metabolites in extracellular fluids. It leads to fast increase in hypoxanthine, xanthine and inosin levels. If the hypoxia duration is longer (chronic hypoxia), these metabolites become pretty sensitive indicator of longlasting hypoxia. Their possibilities as predictors of the severity of hypoxia are still very limited because of the unknown quantity of these metabolites that are transferred from the mother's blood to the infant's blood in utero. In hypoxic circumstances, the glucose metabolism is easy transformed in anaerobic, and the tissue products lactates which have deleterious effect on the brain. 8,9 They worsen the metabolic acidosis, causes endothelial damage and deleterious effect on the brain and circulus vicious starts. There is evidence about the correlation between blood sugar level and clinical manifestation of birth asphyxia, consequent hypoxic-ischemic encephalopathy. Blood sugar level could be increased in the first few minutes, as a result of fast mobilization of glycogen stores deliberation because of increased of catecholamines as a result of stress 10. The glucose is a substrate in the anaerobic metabolism, and as last metabolites lactates are found in enormous quantity in the blood.11 these may cause impairment of bloodbrain barrier and transfer of the fluids in intra and extracellular compartments. In an animal model was shown that brain tissue damage had direct correlation with the brain concentrations of the lactates more than with impaired production of ATP. When ischemia is connected to hypoxia, brain acidosis is increased because the lactates can't be removed and the bicarbonate buffer doesn't work as it has to. The outcome depends on the brain capacity to utilize lactate and ketones as an alternative energy source to

glucose. There isn't evidence that depriving infants of glucose after hypoxia is neuroprotective.

Because of this cascade of negative events, the **AIMS OF THE STUDY** were:

- 1. To present the results of biochemical investigation on blood sugar level (BSL) and lactate level (LL) in the blood of newborns
- 2. To assess the correlation between the levels of glucose and lactate and severity of Hypoxic-ischemic encephalopathy (HIE)

### MATERIAL AND METHODS

Material: newborns born at Obstetric and Gynecology Clinic, in Skopje, Macedonia within a two years' period (2013 and 2014). The patients were grouped as follows:

- 3. control group of 100 healthy full-term newborns, without any indicator of asphyxia, without congenital anomalies, or any other detected abnormality
- 4. examined group, of full-term newborns who survived birth asphyxia and no other pathology

### **Methods used were:**

1. Early detection of birth asphyxia using a scoring system accepted as Evidence based protocol at the Department of Neonatology within Obstetric and Gynecology Clinic in Skopje. It consists of several parameters highly correlated statistically with the severity of birth asphyxia and HIE: fetal heart rate abnormalities, blood gasses from umbilical artery, Apgar score<sup>12</sup>, early Silverman score, meconium stained amniotic fluid and delayed spontaneous respiration. It is based on the The guidelines of the American Academy of Paediatrics (AAP) and the American College of Obstetrics and Gynaecology (ACOG) consider all of the following criteria in diagnosing asphyxia: (i) profound metabolic or mixed acidemia (pH <7.00) in umbilical artery blood sample, if obtained, (ii) persistence of an Apgar score of 0-3 for longer than 5 min, (iii) neonatal neurologic sequelae (e.g., seizures, coma, hypotonia), and (iv) multiple organ

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- involvement (e.g., kidney, lungs, liver, heart, intestines) 13
- 2. Assessment of the severity (depth) of HIE using Sarnat&Sarnat classification of three grades: mild, moderate and severe HIE.
- 3. Biochemical investigations of blood sugar level (BSL) and lactate level (LL) by micro method of the machine.
- 4. Statistical analysis as a part of the software package STATISTICA and Microsoft Excel. For that purpose original database was created for every infant included in the study:
  - a. mean value, standard deviation
  - b. statistical significance (X2 test and Student t-test)
  - c. measures of correlation: Spearman's coefficient of correlation for non-parametric (attributive) indicators

### **RESULTS**

In control group the mean value of BSL was  $2.8\pm0.6$  mmol/l. In the examined group of asphyxiated newborns was  $2.7\pm1.8$  mmol/l. At first sight, they are very similar and almost no difference found. But, it

was a misleading result, because while collecting data it was noticed that there are many variations and unregularly distribution of the particular levels which formed a three modal curve. Because of that, very thorough statistical analysis was performed by subgrouping the infants based on their BSL, as follows:

- a) subgroup of newborns with BSL included in the range of mean value ± 2 Standard deviations of the control values (interval between 1.6 to 4 mmol/l)
- b) subgroup of hypoglycemic newborns with BSL below levels of mean value minus 2 standard deviations
- c) subgroup of newborns with asphyxia with BSL over the mean value plus 2 standard deviations (hyperglycemic)

In subgroup (a) the mean value of BSL was  $3,1\pm0,4$  mmol/l and total of 29 infants examined (33% of all asphyxiated newborns). In the examined subgroup (b) 39 newborns (43%) were included and the mean value of BSL was  $1,3\pm0,2$  mmol/l (hypoglycemic). In the third examined subgroup (c) the rest 21 newborns (24%) were included and mean value of BSL was  $4,8\pm0,4$  mmol/l (Fig 1).

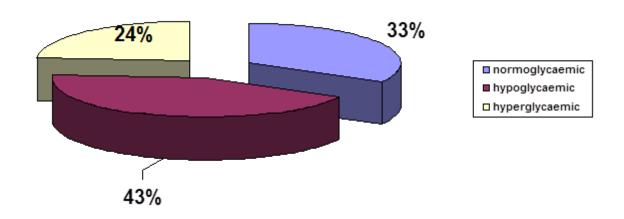


Figure 1 Distribution of the asphyxiated newborns according to the Blood sugar levels

Regarding lactate levels, the results show as follows on Fig 2:

In the control group as a baseline was used the mean value of LL of  $1,5\pm0,3$  mmol/l. The LL in the examined group had very concordant distribution: in

hypoglycemic infants LL was much lower, mean value  $0.9\pm0.06$  mmol/l, similar in normoglycemic infants low level of lactates was found, mean value of  $1.0\pm0.03$  micromol/l, in hyperglycemic the LL increased significantly to  $2.8\pm1.3$  micromol/l.

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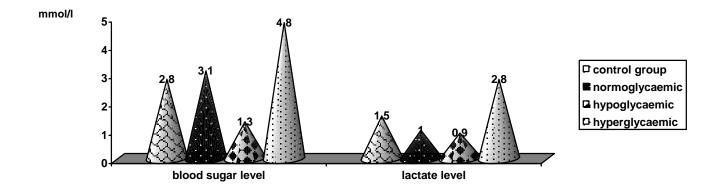


Figure 2: Comparison between the values of Blood sugar levels and Lactate levels

Statistical analysis showed moderate correlation coefficient between the severity of HIE and LL. In the subgroup of infants with mild HIE, the mean value of LL was  $1,6\pm0,3$  mmol/l, in the subgroup of moderate HIE the mean value of LL was  $1,9\pm0,4$  mmol/l and in the subgroup of infants with severe HIE the mean value of LL was  $3,8\pm1,2$  mmol/l. The overall correlation coefficient of Spearman was R=0,65.

### DISCUSSION

Blood sugar level is very important indicator of metabolic activity. Neither hypoglycemia nor hyperglycemia are permissive states for the fragile health of the asphyxiated newborn. Therefore, careful maintenance of this parameter should be performed. And of great importance is the fact that this parameter could be measured and regulated easily even in moderate developed neonatal units.

The lactate level is a little bit more difficult to monitor, although it is of high importance, and is a measure of prolonged hypoxia and impaired glucose metabolism. All units treating such newborns should put efforts to introduce this parameter, because it has moderate coefficient of correlation (Spearman coefficient of correlation of 0,65).

Our results were similar to those found in literature data. Although the significance is not high, it is recommended the investigation of blood sugar levels and if possible blood lactates as auxiliary indicators for the depth of the tissue and metabolic disturbances, due to their tendency for brain damage.

### **CONCLUSION**

Perinatal hypoxia is still important cause of brain damage, and the management of hypoxic baby

includes careful maintenance of glycaemia and other homeostatic parameters.

The present modest research addresses a clinically relevant problem with both paediatric and neuropsychiatric implications. Birth asphyxia is a main cause of newborn death and long-term neurological damage still without a predictive diagnostics, preventive and/or treatment of consensus.

An early diagnosis for predictive diagnostics of asphyxia and hypoxia is of vital importance in planning the short- and long-term care of the infant. The emphasis in neonatology and paediatrics is on non-invasive diagnosis approaches for predictive diagnostics.

Advances in the diagnosis and early predictive biomarkers of perinatal asphyxia, as brain-specific creatin kinase and other neuromodulators, have a promising potential, but still need improvement. Long-term follow-up studies are required to correlate the information obtained with the early predictive biomarkers and clinical-pathophysiological outcome.

Significant in understanding the progress pathophysiology of asphyxia is being achieving, providing a valuable framework on understanding the predisposition to develop metabolic, neuropsychiatric and neurodegenerative diseases at adult stages. It is expected that future studies will allow identification of critical molecular, morphological, physiological and pharmacological parameters, specifying variables that should be considered when planning neonatal care and development programmes.

Emerging targets for early intervention and neuroprotection have been focussed on the inhibition of various potentially destructive molecular pathways including excitotoxicity, inflammation, oxidative stress

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and cell death, and/or therapies that target on restoring functionality of neurocircuitries by stimulation of neurotrophic endogenous properties of the neonatal brain using growth factors and stem cell transplantation. The use of these novel interventions alone or in combination is very attractive and needs further research.

In summary, the individual prediction, targeted prevention and personalised treatments of newborn with asphyctic deficits, is priority in neonatology and paediatrics care. Advanced strategies in development of robust diagnostic, biomarker and potential drugtargets approaches are the main goal for future research. <sup>14</sup>

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