Asphyxia in newborn – risk, prevention and identification of a hypoxic event

Ingrid Brucknerová [1], Eduard Ujházy [2]

1 Department of Neonatal Intensive Care, Faculty of Medicine, Comenius University in Bratislava and Children´s Hospital in Bratislava, Slovak Republic
2 Institute of Experimental Pharmacology & Toxicology, Slovak Academy of Sciences, Bratislava, Slovak Republic

Correspondence to: Assoc. Prof. Ingrid Brucknerová, MD., PhD.
Department of Neonatal Intensive Care
Faculty of Medicine, Comenius University in Bratislava and
Children´s Hospital in Bratislava, Slovak Republic
Limbova 1, 833 40 Bratislava, Slovak Republic.
TEL: +421-259 371 209; E-MAIL: osmium@centrum.sk.

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Abstract

The aim of this review is to present the summarisation of the knowledge about biochemical and clinical changes that occur under the influence of asphyxia as well as about the treatment. Results of experimental works in animal models bring us the explanation about many postasphyxiated changes and help us to understand the pathophysiological changes and consequences of asphyxia.
The authors present the most prominent consequences of neonatal asphyxia in clinical and experimental conditions.
Asphyxia significantly contributes to neonatal morbidity and mortality and determines the prognosis of future development. New insights into the pathophysiology of birth asphyxia provide the opportunity how to prevent permanent damage by the activation of the fundamental molecular processes. Care of newborn asphyxia requires teamwork. Prognosis of the asphyxiated newborn is still dependent on developmental stage (gestational age), the length and intensity of asphyxia, on the level of medical care.

Abbreviations:

ALT	- alanine aminotransferase
AS	- Apgar scoring system
AST	- aspartate aminotransferase
CNS	- central nervous system
SMe1EC2	- 2-ethoxycarbonyl-8-methoxy-2,3,4,4a,5,9b-hexahydro-1 H-pyrido- [4,5b] indolinium chloride
GPX	- glutathione peroxidase
HIE	- hypoxic ischaemic encephalopathy
MDA	- malondialdehyde
MoCoD	- molybdenum deficiency factor
NO	- nitric oxide
TAS	- total antioxidant status
SOD	- superoxide dismutase

REVIEW ARTICLE

INTRODUCTION

It was known at the end of 19th century that short-term interruption of the supply of nutrients does not affect the development of the foetus but the decrease of oxygen supply represented sudden and significant moment for the foetus (Lee 1897). Gradually have improved preventive measures, the monitoring of pregnant women, searching and detection of risk factors that threaten foetal development, also diagnostics have been improved, the new investigative methods and treatment of many diseases were developed. Great progress has been made in neonatal resuscitation, the technique for stimulation of the respiratory and cardiovascular systems as well as treatment were clarified.

In recent years, there is the effort to get the knowledge about biochemical changes that occur under the influence of asphyxia. Results of experimental works in animal models bring us the explanation about many *postasphyxiated* changes. An unresolved issue is the finding of the most sensitive marker of asphyxia, which would determine the length and intensity of asphyxia, as well as of the indicator of the degree of damage and determining prognosis. Asphyxia is not a separate clinical entity, not a symptom, but it is a syndrome, which significantly affects morbidity, mortality and determines the prognosis of future development.

ASPHYXIATED NEWBORN

Definition

Asphyxia, a term adapted from the Greek language expresses "pulseless" status, as opposed to the term of birth asphyxia, which is used more often and indicates the presence of a hypoxic-ischaemic event. Asphyxia is a condition in which the body is subjected to a time of foetal hypoxia and/or reduced tissue perfusion (ischaemia). When an imbalance between the total amount of antioxidants and free radicals is presented, the oxidative stress is activated (Griffioen *et al.* 2007; Brucknerová *et al.* 2005a,b; Tsukahara 2007). Recently the oxidative stress was re-defined as the state where redox regulation of cellar signaling and redox-sensitive control of cellular functions is disrupted. The common feature of hypoxic ischaemic injury is an insufficient oxygen supply to the central nervous system (CNS). Areas of cell injury in the brain are depended on the intensity and duration of hypoxic insult, vulnerability of nerve cells and of gestational age of newborn.

Hypoxic-ischaemic condition presents a heterogeneous group of clinical symptoms that formed the syndrome. There are many biochemical changes, but till this day there are not precisely defined markers which distinguish the perinatal asphyxia (Garcia-Alix *et al.* 1993; Carter *et al.* 1993; Koc *et al.* 1998; Bracci *et al.* 2006; Delivorias-Papadopoulos & Mishra 1998; Saugstad 1998; Thornberg *et al.* 1995a; Siciarz *et al.* 2001; Arguelles *et al.* 2006). The presence of one pathological condition is not an indication of asphyxia. According to American College of Obstetrics and Gynecology and American Academy of Pediatrics essential criteria to define an acute *intrapartum* event sufficient to cause cerebral palsy (must meet all four) are (Hankins & Speer; 2003):

- evidence of a metabolic acidosis in foetal umbilical cord arterial blood obtained at delivery (pH less than 7 and base deficit of at least 12 mmol/l),
- early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation,
- cerebral palsy of the spastic quadriplegic or dyskinetic type,
- exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

Apgar scoring system

The Apgar scoring system (AS) as a simple method of investigation of the newborn during the first, fifth and tenth minute of life evaluating five basic signs was officially presented in 1952 (Brucknerová *et al.* 2012). By using this method we can classify the newborn as vital or asphyxiated. Physical investigation of the youngest child, particularly of the newborn just after delivery can have a predictive value for its future development. The "optimal" value of AS does not exclude the development of hypoxic-ischaemic encephalopathy, but the low level of AS together with the presence of risk factors leads to the formation of hypoxic-ischemic encephalopathy (Gardianová *et al.* 1996; Brucknerová *et al.* 2009, 2014; MacLennan; 1999).

Incidence of asphyxia

Perinatal asphyxia is also in the 21st century a serious threat to the newborn. It contributes to neonatal morbidity and mortality. In ranking of the most important causes of infant mortality it is still on second place just after infection. At the same time it is also one of the major causes of acquired brain injury in neonates (Brucknerova & Benedeková 2000b; Bryce *et al.* 2006). According to Levene *et al.* (1985), Thornberg *et al.* (1995b), in industrialized countries, death or severe neurological damage due to perinatal asphyxia occurs in 0.5 to 1.0 per 1 000 live births. In developing countries, perinatal asphyxia occurs more frequently and is a major cause of perinatal mortality. According to data Airede (1991), Singh *et al.* (1991) and Oswyn *et al.* (2000), asphyxia occurs in up to 5–50 per 1000 live newborns. The aim in 1997 was that the incidence ranged from 0.1 to 0.2 per 1000 live births with a birth weight of 1 500 g (Wolf 2002).

The symposium Programme for global research in pediatrics (Programme for Global Paediatric Research) in 2005, which was dedicated to asphyxia, data on the number of neonatal deaths to perinatal asphyxia were published. The numbers were startling. Asphyxia is

still a serious global problem. Approximately one million newborns die every year due to "birth asphyxia." Although the overall mortality rate is falling, from the total number of children who died, newborns form 1/3. It represents 3.9 million newborns. In addition to total high incidence of neonatal mortality there is still very high incidence of stillborn foetuses on the one hand and on the other hand, children who survived have to contend with lifelong mental and physical disabilities. At the same time, it is estimated that about one million children are monitored for neurological postasphyxiated "problems". It is generally considered that the main causes of death include prematurity (28%), severe infections (26%) and asphyxia (23%) (Lawn *et al.* 2005, 2011; Saugstad 2005).

Each year an estimated 814 000 children die of intrapartum-related causes. Intrapartum-related neonatal deaths are the fifth most common cause of under-five child deaths after pneumonia, diarrhea, preterm birth complications, and neonatal infections (Black *et al.* 2010).

Etiology

The causes of asphyxia are different. Generally they can be divided into 5 main groups:

1. mother's disease associated with inadequate oxygenation of blood,
2. reduction of blood flow from the placenta to the mother's body (abnormal regulation of blood pressure – hypotension, hypertension, maternal, placental pathologic contractions, status epilepticus),
3. inadequate blood flow from the placenta to the foetal body,
4. failure gas exchange in the placenta,
5. condition in the foetus associated with increased demands for oxygen (anaemia, infection, hydrops).

From these aetiologic factors in 90% of the causes of asphyxia occurs prenatally and during labour, and only the remaining 10% postnatally. The foetus can be exposed to acute or chronic hypoxia. In severe conditions of acute asphyxia the death of the foetus may occur. The second type of asphyxia is chronic one. In contrast to acute hypoxia its intensity is modest. In many cases only clinical and neurological symptoms in the early neonatal period confirm the presence of perinatal asphyxia.

Evaluation of anamnestic data with respect to the presence of asphyxia, and especially actively detection for risk medical history data is a prerequisite for early detection of impending asphyxia.

Patogenesis

Decrease of the oxygen content in the blood (hypoxaemia) and tissues (hypoxia) adversely affects on the entire body, but especially on the CNS (phase of primary damage). Attenuation of respiratory centers in the brain stem that regulate lung ventilation closes vicious circle, which, if not interrupted, can end up with neonatal death.

If after the stage of hypoxaemia and tissue's hypoxia, there is a reduction or complete interruption of blood flow, the phase of ischaemia will occur (phase of secondary damage). Currently, much attention is paid to the role of reperfusion injury, which involves mainly formation of free oxygen radicals, release of excitatory amino acids, etc. (phase of terciary damage). This fact was the basis for consideration, that asphyxia belongs among so-called free radical diseases. Mechanisms throught which free radicals pursue their influence on cell were the aim of many research works, but still are not yet completely clear (Saugstad 1998a, 2004; Ďuračková 1998; Ďuračková *et al.* 1999; Ohki *et al.* 2001; Vento *et al.* 2001a, 2001b). Precisely identification of mechanisms of participation and the impact of free radicals and reactive metabolites opens for us new opportunities for prevention, diagnosis and treatment, not only in experimental models but also in neonates as it is possible in adult cardiac surgical patients (Pecháň *et al.* 1996; Holomáň & Pecháň 2002; Milner 1998; Shoji & Koletzko 2007).

MODEL SITUATIONS OF ASPHYXIA IN THE EXPERIMENT

The study of oxidative stress uses various biomodels, model situations in animals with which we identify and examine the basic pathomechanisms leading to damage of tissues and organs. Model situations are also used for evaluation of effects and mechanisms of action of various natural or synthetic antioxidant active substances (Dubovický *et al.* 2008; Mach *et al.* 2009).

Developmental toxicology

The reliability and extent of the tests depend mainly on the choice of methods and experience of the laboratory where the test is conducted. Using currently available methods, which are based on the basic teratology research, is possible to identify most of the potential harmful substances, to identify the size (range) of the embryotoxic dose and to identify relationships between dose and its effects (Ujházy *et al.* 2005a, 2005c, 2008, 2012, 2013).

Antioxidant treatment in rat models of asphyxia

One of the promising antioxidant is 2-ethoxycarbonyl-8-methoxy-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,5b] indolinium chloride (SMe1EC2). It is a substance with proven cardioprotective, neuroprotective effects, of high antioxidant properties and with no embryotoxic and teratogenic capability (Sotnikova *et al.* 1998; Ujhazy *et al.* 2008). It was found that the administration of SMe1EC2 to pregnant rats may extent the foetal injury by oxidative stress, which has been induced during the administration of phenytoin during prenatal development. Antioxidant effect of melatonin did not

prevent the formation of teratogenic effect provoked by phenytoin (increased incidence of cervical spine vertebral anomalies). Antioxidant influence of SMe1EC2 had manifested by protective action on placental and foetal weight, by positive impact on reproductive characteristics (increased number of surviving foetuses, reduced number of pre-implantation and post-implantation losses and the number of resorptions). The protective effect on skeletal anomalies of SMe1EC2 (ribs, vertebrae, tail), although not statistically significant are shown in the total number of abnormalities of the cervical vertebrae. SMe1EC2 pretreatment significantly reduces the incidence of skeletal anomalies, increases the weight of the placenta and foetus, and partially reduces the number of visceral anomalies (Ujházy *et al.* 2004, 2005b, 2006a, 2008; Dubovický *et al.* 2007).

Based on literature results, we can assume that the "pre-treatment" of pregnant rats with SMe1EC2 can prevent extent of expressions of embryo-foetal toxicity, which is induced by chronic intrauterine hypoxia induced by phenytoin. Importance and significance of complex factors, which consists of protective effects of SMe1EC2 in combination with other antioxidant active ingredients, proper timing of initiation of therapy, the correct functioning of the placenta as well as the interaction between maternal and foetal metabolism will form a very important protective complex.

Final recommendations for the us of antioxidants in the prevention of oxidative stress during pregnancy, however, need further studies**.**

EFFECT OF ASPHYXIA ON THE FUNCTION OF ORGANS AND BODY SYSTEMS IN NEWBORN

The consequences of the impact of asphyxia on the newborn organism are different. The degree and nature of the damage depends mainly on the gestational age of the newborn, the intensity of asphyxia, and the site of action. The biggest problem is the accurate determination of the duration of asphyxia (Pourcyrous 1999). In many cases we are not able to detect the beginning of the onset of action of asphyxia insult, the duration, frequency, severity, and to determine the precise temporal characteristics. In such cases, the severity of asphyxia is judged by the extent and severity of complications.

1. Central nervous system

The central nervous system is control and integral system of organism. The sensitivity of nervous cells to hypoxia changes during development, and thus the CNS's consequences to asphyxia depend on the degree of maturity and differentiation of cells, and on the reference to glial cells. In a case of preterm newborns the most sensitive are cells of brain stem, because in cerebral cortex an anaerobic metabolism is dominant. Many works confirmed that the consumption of oxygen in cerebral cortex rises at the end of pregnancy. Due to this reason at the end of physiological pregnancy, in term newborn the most sensitive is the area of cerebral cortex.

Perinatal brain damage in term neonates is caused by the reduction of blood flow in the umbilical cord or in uterus. To the lack of oxygen at the beginning of asphyxia foetus responds by activating of sympathetic adrenergic system without changes of cardiac output. In the body there is a regional selective vasoconstriction with a reduction in blood flow to organs and tissues, which has a lower intensity of metabolism (intestine, kidneys, muscles and skin). Foetal circulation ensures increased blood flow to vital organs (CNS, heart, adrenal gland). To the difference in damage of CNS cells may contribute the different density of sympathetic nerve endings. Asphyxia, a powerful stimulator of sympathetic adrenergic system can lead to greater vasoconstriction in the area of blood supply of anterior cerebral artery in comparison with the structures, which supplies the basilar artery (cerebellum, brainstem, part of the brain). However asphyxia persists, the foetus is no longer able to continue to maintain circulatory centralization. The cardiac output decreases as well as the size of the brain blood flow. After the failure of the self-regulatory ability of the brain the flow becomes dependent on blood pressure. During ischaemia many metabolic and circulatory changes occur (decreased activity of oxidative phosphorylation, "calcium" overloading in cells, excitatory amino acids – glutamate, aspartate; nitric oxide). Theory of "calcium overload" in cells leads to increased amount of lipase, nitric oxide (NO) synthase, proteases, and endonucleases. As a result of reduced blood flow in ischaemic tissue erythrocytes (agglutination), leukocytes (increased adhesion, increased reactive metabolites, increased reactive metabolites of nitrogen, increased peroxidases, and increased proteases) and platelets (aggregation) are activated. The consequence of these changes is the presence of increased viscosity of the blood. An uncontroled formation of free radicals is then presented in the phase of reperfusion and reoxygenation. To damage of cells contributes also an accelerated timing cell death (apoptosis), ion imbalance and damage of cellular defensive mechanisms.

The most serious complication of asphyxia is brain involvement: hypoxic-ischaemic encephalopathy, oedema of the brain, and atrophic hydrocephalus. The clinical picture of asphyxia in term neonates may experience following symptoms: seizure activity, changes in muscular tension, bleeding, apnoea, and brain death (Lackman & Tollner 1995; Hagberg *et al.* 1998; Ikeda *et al.* 1999; Brucknerova & Benedeková, 2000; Inanc *et al.* 2005; Perlman 2006).

The presence of seizure activity during the first hours of life is one of the typical manifestations of CNS damage due to asphyxia. For convulsion activity may hide early form of molybdenum deficiency factor (MoCoD). The presence of molybdenum is essential for the function of xanthine oxidase, aldehyde oxidase and sulfite oxi-

dase. Deficit of MoCoD with subsequent accumulation of toxic sulfite in the brain causes the seizure activity refractory to treatment and severe rapidly progressing encephalopathy of metabolic origin (Brucknerová *et al.* 2010). Another cause of seizure activity and marks of "toxic" encephalopathy are organic acidurias (Bzdúch *et al.* 2005, 2007).

2. Cardiovascular system

The heart begins to work since the end of the third gestational week. Heart activity provides and maintains the circulation of the foetus and of the foetal placental circulation. Cardiovascular system, along with other body systems ensures smooth adaptation to extrauterine life changes. Disability of cardiovascular system under the influence of asphyxia can manifest as prenatal and/or postnatal arrhythmias, myocardial dysfunction syndrome and transient myocardial ischemia with insufficiency of tricuspid valve (Pollin & Fox 1992a, b; Barberi *et al.* 1999; Brucknerová & Benedeková 2000; Illíková *et al.* 2013).

Rhythm disorder in the foetus is a manifestation of a serious threat. Foetal heart rate is an indirect indicator of foetal CNS activity, oxygenation and acid-base balance. Baseline foetal heart rate is among 110–160 beats/min. Normal variability is 5–10 beats/min. One of the causes of reversible intrauterine and postnatal paroxysmal tachycardia can be acute asphyxia and adnate infection (Brucknerová *et al.* 1996). In some cases, the clinical manifestations in unrecognized paroxysms of tachycardia during intrauterine development may overlap or enhance the appearance of acute asphyxia. Most often reentry tachycardia is occured, with various forms of Wolff-Parkinson-White syndrome (Allan *et al.* 1984; Azancot-Benistry *et al.* 1992; Parilla *et al.* 1996; Strasburger 2000; Brucknerová *et al.* 2009). Intrauterine bradycardia (less than 100 beats/min. for 1–2 minutes) has been a reflection of prolonged distress, direct injury to the myocardium, or systemic disease maternal (Brucknerová *et al.* 2007). Congenital anomaly of excitomotor system of the heart or congenital heart disease can also cause intrauterine arrhythmias.

Rhythm disorder in a newborn asphyxia belongs among the indirect signs of previous asphyxia. It can be manifested by a decrease, respectively by reductions of heart rate below the lower limit of normal. Decrease in the value below 80 beats/minute is typical for severe asphyxia (Brucknerová *et al.* 2009). In the most severe cases we can find the picture of severe heart failure, as presented in the case of a patient with neonatal form of carnitine palmitoyltransferase II deficiency, which is considered to be invariably fatal (Demaugre *et al.* 1991; DiMauro *et al.* 1973; Smeets *et al.* 2003; Vekemans *et al.* 2003; Brucknerová *et al.* 2008a).

Myocardial dysfunction syndrome – syndrome of low systemic perfusion occurs in premature and mature newborns. Myocardial dysfunction leads to a reduction in muscle contractility of the left ventricle, to increasing of end-diastolic pressure and acute reduction of cardiac output (systemic hypoperfusion). Reduction in systemic blood flow leads to the development of metabolic acidosis. In addition to the above mentioned changes atrioventricular valvular insufficiency may be present. It occurs mainly in cases of severe asphyxia.

Transient myocardial ischaemia with tricuspid insufficiency is another consequence of asphyxia due to damage of papillary muscles, leading to valvular insufficiency (Pollin & Fox 1992b).

3. Respiratory system

Respiratory system provides many vital functions; the most important function is the transport and the exchange of respiratory gases. During intrauterine development the placenta is a place of blood gas exchange. First signs of respiratory activity we can detect at the 14th gestational week. There are active and rhythmic contractions of the respiratory muscles, particularly of the diaphragm, which are associated with movements of the thoracic and abdominal wall of the foetus. The influemce of asphyxia on respiratory system may manifest as a syndrome of persistent pulmonary hypertension, pulmonary atelectasis or emphysema, pneumothorax, pulmonary oedema, pulmonary haemorrhage, meconium aspiration, surfactant deficiency and apnoea (Lackman 1996).

Under the picture of respiratory insufficiency after exclusion of primary pulmonary cause and asphyxia it is necessary for the differential diagnosis to exclude congenital heart disease, sepsis, metabolic disease or birth trauma.

4. Gastrointestinal system

Activity of the digestive system is presented from 16th–20th gestational week. The main functions of the digestive system are secretory, motor and resorption. The adequate flow of oxygenated blood affects growth, development and function of individual parts of the digestive system. To the wide range of digestive complications of asphyxia belong: necrotising enterocolitis, acute necrosis of the stomach and/or bowel perforation, acute stomach and/or intestines, hypoxic liver damage. In the case of inflammatory bowel necrosis asphyxia is the second leading cause of it.

From a biochemical point of view, it is valuable to analyze the hypoxic damage of liver cells by examination of values of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and by setting the value of the quotient DeRitis (AST/ALT) to determine the degree of damage to liver cells. In liver cells, 60% of AST is located in the cytoplasm and 40% in the mitochondria. ALT has the highest activity in the liver cell; where in the cytoplasm a concentration is of 10 000 times higher than in plasma. In addition, ALT is located in the heart and skeletal muscle, and kidney (Ferenčík *et al.* 2000; Tarcan *et al.* 2007). Examination of both enzymes is particularly useful in situations where we expect the

current disability of liver and heart, in cardiogenic shock and in severe hepatic impairment (Brucknerová *et al.* 2005a, 2005b, 2010; Gupte *et al.* 2011).

5. Urinary system

Individual sections of the urinary tract take part in maintaining homeostasis, regulate the volume and composition of body fluids and are involved in the removal of various metabolites, and blood pressure regulation. Newborn kidneys are functionally and morphologically immature; the stage of maturity depends on the gestational age. These differences are due to the reduction in blood flow of the kidney, morphological immaturity of the nephron and due to disproportion in glomerulotubular relations. Hypoxia, shock state, hypovolemia, hyperviscosity affect the function of kidneys (Gupta *et al.* 2005; Aggarwal *et al.* 2005; Tekin *et al.* 2007).

Renal damage belongs among most frequent complications of asphyxia. Currently, we distinguish the following clinical entities: acute renal insufficiency, syndrome of inappropriate antidiuretic hormone secretion, acute renal tubular or cortex necrosis, acute necrosis of renal medull and haematuria (Vachvanichsanong *et al.* 2012).

6. Retina

Extent of postasphyxiated changes of newborn adds retinal vascular involvement. Although retinopathy is more frequent complication in newborns born prematurely, it also occurs in term infants who have experienced a significant degree of asphyxia. An incomplete vascularization of retina explains the occurrence of retinopathy in term neonates.

Risk factors for retinopathy include not only prematurity, but also high or low oxygen concentration, status after resuscitation, sepsis, repeated administration of blood derivatives, artificial pulmonary ventilation, variations in concentrations of minerals in blood, repeated decreasing in oxygen saturation, acidosis, arrhythmias, pressure imbalance, etc. Of these risk factors, especially changes in the amount of oxygen are considered to be a key moment in the pathogenesis of retinopathy (Yasuto *et al.* 2000; Brucknerova & Benedeková 2000).

7. Haematopoietic system

Complications of asphyxia in the newborn also include the involvement of blood elements. Asphyxia can change the biophysical properties of blood and can cause changes in properties, structure and functions of red blood cells and platelets (Fahnenstich *et al.* 1995; Phelan *et al.* 1995; Pollak *et al.* 2001; Curtin *et al.* 2002; Braci *et al.* 2006; Tomar *et al.* 2011). Haematologic changes after birth can indicate the approximate duration of hypoxemia (acute vs. chronic) (Brucknerová *et al.* 2008b). In case of asphyxia increased number of leukocytes within the first 96 hours of life is associated with an increased risk development of pathology (Morkos *et al.* 2007). Phelan *et al.* (2007), indicate that thrombocytopenia is not typical for acute asphyxia, and it is not a sensitive marker for mild degree of acute asphyxia.

Presentation of asphyxia and acute blood loss has some common symptoms. In the foreground they are accompanied by tachycardia, fluctuations in blood pressure and peripheral cyanosis. Additional features include signs of respiratory insufficiency in the form of rapid and shallow breathing, and severe anaemia confirmed by low haemoglobin and red blood cells. Haemolytic disease of the newborn confirms unconjugated hyperbilirubinaemia, enlargement of the liver, in some cases enlargement of the spleen and positive Coombs test in process of isoimunisation.

8. Internal environment

Effect of asphyxia on some parametres of oxidative stress (malondialdehyde, MDA)

To damage of biological membranes may contribute free radicals and reactive metabolites (Kaya *et al.* 2000). The process of lipid peroxidation leads to oxidative damage of polyunsaturated fatty acids. A result of the process of peroxidation of lipids is the formation of hydroxyperoxides and a full range of secondary metabolites (aldehydes, ketones). Among the most important we include MDA, aldehydes, hexanal and 4-hydroxynonenal. MDA is considered to be the end product of lipid peroxidation (Singh *et al.* 1999; Basu *et al.* 1999; Yigit *et al.* 2000; Mihailovic *et al.* 2000; Wardle *et al.* 2002; Bebernitz & Schuster 2002; Bouhafs *et al.* 2000).

In accordance with the findings from world literature the determination of degradation products of lipid peroxidation in the venous blood, MDA, we can include among the biochemical methods for diagnosis of perinatal asphyxia (Brucknerová *et al.* 2004, 2006).

Effect of asphyxia on the antioxidant system

Antioxidant protective system is the set of all active antioxidant substances in the body (total antioxidant status, TAS). TAS can operate on several levels: prevents the formation of free radicals, scavenges free radicals, inhibits the re-conversion to reactive metabolites, converts reactive forms to less reactive forms, removes free radicals and helps to remove damaged molecules (Batra *et al.* 2000; Molicky *et al.* 2001; Brucknerová *et al.* 2004, 2006, Minghetti *et al.* 2011; Upadhyaya *et al.* 2005; Rokyta *et al.* 2008).

To the TAS belong also two intracellular antioxidants: superoxide dismutase (SOD) and glutathione peroxidase (GPX). SOD is metaloenzyme with a protective effect on the body. In the red blood cells SOD is a part of the primary antioxidant protection system, and also operates in haemoglobin autooxidation during which generates superoxide radical. GPX catalyzes the reaction with the hydrogen peroxide and organic peroxides. There are two types of GPX in relation to selenium. GPX has significant antioxidant effect just by changing the hydrogen peroxide to water and prevents formation of dangerous hydroxyl radical.

Effect of asphyxia on blood glucose and ionized calcium

From changes in the internal environment of the newborn hypoglycaemia, hypocalcaemia, hyponatraemia, acidosis and hypoxaemia are most common. Hypoxia and ischaemia triggers the cascade of biochemical reactions. One of the changes is the cell membrane depolarization with transcellular ion pump failure, accumulation of calcium ions in the cell cytosol. Due to energetic failure of cells, acidosis, free oxygen radicals, lipid peroxidation of cell's membrane and accumulation of calcium disrupting of cell structure to her death can happened (Brucknerová & Benedeková, 2000).

THERAPY

The main aim of the treatment in asphyxiated newborn is the neuroprotection therapy. During last years many studies were published about therapeutic hypothermia, its advantages and disadvantages. Strong hypoxic-ischaemic insult can cause the development of hypoxic ischaemic encephalopathy (HIE). Clinical management of HIE consists of therapeutic hypothermia (indications: ≥36 completed weeks of gestation and less than 6 hours of life; and one of the following findings: Apgar score of ≤5 at 10 minutes after birth or continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth or acidosis – pH ≤7.00 in umbilical cord or any blood sample within 60 minutes of birth or base deficit ≥16 mmol/l in umbilical cord or any blood sample; and seizures or altered state with reduced or absent response to stimulation plus abnormal reflexes plus focal or general hypotonia) and supportive management (cardiovascular – dopamine, dobutamine and respiratory support; anticonvulsant therapy – phenobarbital loading dose 20 mg/kg; followed by 1.5–2.5 mg/kg every 12 hours; prevention of infection; analgesic and sedative therapy; fluid management). A part of therapy in a case of persistent pulmonary hypertension can be also inhaled NO. Cooling is not appropriate if the newborn is likely to require surgery during the first 3 days after birth or there are other abnormalities indicative of poor long term outcome. There is a lack of data about the use of cooling for neuroprotection in infants of lower gestational age or for other conditions as well as in newborns beyond 12 hours of life (Guidelines for Management of Infants with Suspected Hypoxic Ischaemic Encephalopathy, 2011; Cavallaro *et al.* 2013).

The newborn during whole body hypothermia following analysis must be monitored: body temperature (skin temperature, rectal/oesophageal probe), heart frequency, respiratory rate, oxygen saturation, blood pressure (noninvasive/invasive), urine production, and electrocardiogram and electroencephalogram. Neuroimaging methods can help us to detect the structural changes (ultrasonography, magnetic resonance imaging).

PREVENTION OF NEONATAL ASPHYXIA

Despite the continuous improvement of the medical care and high technology innovations which have been developed to manage and improve the outcomes of asphyxiated newborns in the last decade we are still talking about the absence of a satisfactory effective treatment of asphyxia. Great perspective is the inclusion of controlled and regulated hibernation by well-trained team in combination of specific anticonvulsant treatment (Van den Broek *et al.* 2013; Cavallaro *et al.* 2013). To achieve the satisfactory prevention is essential continuously improvement of methods of investigation so as not to endanger either the mother or the foetus and to allow accurate capture deviation from normal development as it is for example in maternal corticosteroids administration (Grzesiak *et al.* 2013 a, b). In detection of asphyxia helpful is the finding of the best parameter and its proper evaluation.

In general we can distinguish three forms of prevention. Primary prevention of asphyxia means the improvement of maternal health including nutritional status, prenatal recognition of at-risk pregnancies, and skilled attendance at birth. Secondary prevention consists of a prompt and effective resuscitation. Tertiary prevention is connected with the management and treatment of neonatal postasphyxiated complications (Lawn *et al.* 2009).

SUMMARY AND CONCLUSION

This work presents summary of knowledge about the issue of asphyxia in the newborn, which significantly contributes to neonatal morbidity and mortality.

New insights into the pathophysiology of birth asphyxia provide the opportunity how to prevent permanent damage by the activation of the fundamental molecular processes. The problem still remains that there is no a clear and precise definition of asphyxia. Finally, we emphasize the importance of a comprehensive vision of newborn asphyxia. Newborn organism is formed by organs systems, whose activity is interconnected. Many times history, clinical or biochemical images do not reflect the actual condition of the sick newborn, but through knowledge of the interdependencies allow us an early recognition of asphyxia and sensitive election of healing process.

Care of newborn asphyxia requires teamwork. Prognosis of the asphyxiated newborn is still dependent on the length and intensity of asphyxia, on the level of medical care.

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