

# Foetal asphyxia as a strong stimulator of the sympathetic nervous system in the brain

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## Abstract

The aim of the study was to analyse case report of prenatally unknown asphyxia of the foetus (a preterm newborn from the second pregnancy delivered by urgent caesarean section in 31st gestational week; birth weight 850 grams, birth length 41 cm, value of Apgar score 7/8) with signs of respiratory insufficiency immediately after birth with hypotonicity.

The authors present the case of postnatal at the 1st day of life assessed cystic malformation in the brain of premature newborn. They emphasize the importance of detailed prenatal investigation as most important in preventing prenatal asphyxia and consequent complications. Central nervous system and especially white matter of the brain of the newborn is most vulnerable area of the brain. Together with oxidative stress after exceeding of antioxidant capacity belong among main factors that play an important role in the pathogenesis of hypoxic-ischemic encephalopathy.

## INTRODUCTION

The central nervous system (CNS) is control and integrating system in the body. It consists of a set of specialised structures that ensure fast and accurate transfer of information from the receptors, their central processing and transmitting signals to the executive organs.

Nerve cells need for service adequate supply of oxygenated blood, affecting not only the brain perfusion pressure, but also the biophysical properties of blood and the vascular properties of the network itself.

Damage of the nerve cells can be due to haematological causes (acute haemorrhage; hyperviscosity; coagulopathies), infection, vascular problems (thrombosis; embolism), metabolic disorder, maternal systemic disease (autoimmune disorder) and is the most serious consequence of asphyxia (arterial infarction) (Dlamini *et al.* 2010; Brucknerová *et al.* 2014; 2011; Brucknerová & Ujházy 2014). The sensitivity of the brain cells to hypoxia varies during development, and therefore the consequences of asphyxia depend on the degree of maturity and differentiation of cells as well as on relationship to glial cells, regulation of blood flow,

the maturity of blood-brain barrier, degree of myelination, blood viscosity and cardiac output.

The majority of published international works describes forms and consequences of CNS damage (Rutherford 2002; Lani *et al.* 2011; Miller, 2000). Neonatal cerebral infarcts, relatively common conditions with a prevalence of 1 in 4,000 live births, usually present with neonatal seizures alone or together with various neurologic findings (Akman *et al.* 2003). Among newborns described by Estan & Hope, 1997, cerebral infarction was the second commonest cause of seizures in neonates over 31 weeks of gestation.

## INFLUENCE OF ASPHYXIA ON CNS

### Failure of circulation in preserved autoregulation

Perinatal brain damage in term newborns after severe asphyxia is preceded by a reduction of blood supply in the uterus or in umbilical cord. The foetus responds to the lack of oxygen at the beginning of asphyxia by acting of the sympathetic nervous system at unchanged size of cardiac output. In the body is selectively vasoconstriction appears (centralization of circulation) with reduction of blood supply to organs and tissues with lower intensity of metabolism (intestine, kidneys, muscles and skin) (Brucknerová & Ujházy 2014). The total consumption of oxygen decreases. Foetal circulation ensures increased blood flow into vital organs (CNS, heart, adrenal glands). Foetus with higher blood flow maintains optimal supply of oxygen and nutrients.

The different density of sympathetic nervous endings can contribute to different damage of the cells of CNS. Asphyxia as a strong stimulator of the sympathetic nervous system may induce pronounced vasoconstriction in the area of arteria cerebri anterior in comparison with structures supplied by arteria basilaris (cerebellum, brain stem, part of the cerebri) (Holomáňová & Brucknerová 2003). However asphyxia remains, foetus is not able to maintain circulatory centralisation. Cardiac output and the brain blood supply decreases, changes in blood content are presented.

### Failure of circulation with worsened autoregulation

Brain vessels have the ability to autoregulate the blood supply; it means they are able to maintain constant blood flow despite changed values of blood pressure. The autoregulation depends on concentration of hydrogen and potassium ions and pCO<sub>2</sub> in the cells of smooth muscles in vessels. Decrease of the pO<sub>2</sub> and increase of the pCO<sub>2</sub> lead to vasodilatation of arteries.

The process of autoregulation during asphyxia is destroyed. It depends on blood pressure. Decrease of blood pressure is followed by decreased blood flow through the brain and ischaemia occurs.

### Damage of endothelial cells during hypoxia-ischaemia

Many metabolic changes are presented during ischaemia. Systemic blood pressure and blood viscosity

are main regulatory factors of blood flow in the ischaemic area, which is presented with lack of oxygen, decreased amount of energetic substrates, decreased removal of CO<sub>2</sub>, and increased formation of the lactate. The process of ischaemia activates many biochemical and circulatory changes (decrease activity of oxidative phosphorylation; failure of the Na<sup>+</sup>/K<sup>+</sup> pump; inflow of calcium ions through calcium channels into the cells; increased amount of excitatory amino-acids – glutamate, aspartate; activation of N-methyl-D-aspartate receptors; activation of lipases, NO synthetase, proteases, endonucleases and formation of free radicals) (Brucknerová *et al.* 2010).

## CHANGES IN BLOOD

Erythrocytes, leucocytes and platelets are activated as consequence of the decrease blood perfusion in ischaemic tissue (decreased blood perfusion, loss of autoregulation, decreased energy intake, decreased O<sub>2</sub>). Huge amount of vaso-active substances and free radicals are released. Increased aggregation is typical for erythrocytes. Increased adhesion, formation of O<sub>2</sub> and nitrogen reactive radicals, peroxidases and neutral proteases are typical for leucocytes. Platelets have tendency for increased aggregation. These changes increase blood viscosity and disturbance of blood flow in the capillaries is presented. Degree of ischaemia is worsening due to their influences and death of cells is present.

Cells of brain stem are sensitive in premature newborns. In the brain cortex in that time an anaerobic metabolism of carbohydrates is dominant. The utilisation of oxygen in brain cortex increases at the end of pregnancy that is why damage of brain cortex is typical in term newborn during hypoxia (Delivoria-Papadopoulos & Mishra, 1998). Under influence of asphyxia reversible or in long lasting hypoxia an irreversible damage can occur.

The subsequent neurological problems in newborn after asphyxia can be presented as seizures, hypotonicity or hypertonicity. To the risk factors belong gestational age, cause of infarction, and intensity of additional clinical problems (cardiovascular, respiratory). Foetal and neonatal human brain contains more water than myelinated, mature brain.

Three basic patterns are described in term newborns: diffuse neuronal injury (after very severe and very prolonged insult); cerebral – deep nuclear disease (damage of basal ganglia and thalamus); deep nuclear brain stem disease (damage of brain stem); pontosubicular and cerebellar injury (Volpe 2008).

From the pathomechanism of development of nervous cell damage is known that cytoplasmic vacuolation caused by mitochondrial swelling occurs within 5 to 30 minutes after the onset of hypoxia. Neuronal cells are also very sensitive to glucose. According to Vople (2008), the order of vulnerability is neuron – oligodendroglia – astrocyte – microglia. After 24 to

36 hours (eosinophilia of neuronal cytoplasm, loss of Nissl substance, fragmentation of nuclei; breakdown of plasma and nuclear membranes is present. Brain of premature newborn has immature cortical neurons and relative lack of Nissl substance. Process of physiological apoptosis contributes to neuronal cell death. Processes of apoptosis together with process of necrosis are presented together in hypoxic-ischaemic disease.

For premature newborn is typical involvement of grey matter injury – deep nuclear structures. Involvement of brain stem may occur in combination with basal ganglia and thalamic involvement. In premature newborn with extremely low birth weight cerebellar injury is typical.

Term newborns have better differentiated neurons of calcarine cortex and the precentral and postcentral cortices (involvement of cerebral cortex is typical and later cerebral white matter injury). In very severe asphyxia also neurons in the depths of cerebral sulci are affected. Influence of intensity of blood flow and blood supply (most sensitive areas are border zones) is also very important (Akman *et al.* 2003; Estan & Hope, 1997; Miller, 2000; Mercuri *et al.* 2002).

The consequences of asphyxia can be confirmed not only postnatally, but also prenatally.

## CASE REPORT

The aim of the study was to analyze the case report of a prenatally unknown asphyxia of the foetus. Patient was a preterm newborn from the second pregnancy (1 $\times$  abortus) of nonconsanguineous parents. Mother was monitored for Morbus Recklinghausen since 3rd year of life. Newborn was delivered by urgent caesarean section (eclampsia; hypotrophy of the foetus) in the 31<sup>st</sup> gestational week (birth weight 850 grams, birth length 41 cm, value of Apgar score 7/8/8) with signs of respiratory insufficiency immediately after birth and generalised hypotonicity. Immediately after delivery the newborn's respiration was stimulated with ambu bag and administration of oxygen was used.

Newborn was 24 hours on ventilatory support with maximal oxygen dependence of 30%.

In clinical picture hypotonic syndrome was confirmed since birth. Transfontanelle ultrasound confirmed zone of infarct in periventricular area on the left side, subependymal haemorrhage with extension to the surrounding area (2 $\times$ 1.5 cm) with dilated lateral ventricles. Brain structure was very immature. The final ultrasound control after 30 days confirmed asymmetric dilatation of ventricular system (right lateral ventricle was very thin, left lateral ventricle with diameter 1.3 cm), infarct lesion above frontal horn (<2 cm) in fronto-temporal area is not spread to cortical zone and ventricles with hyperechogenic borders. The head circumference was in normal range. Final neurological examination confirmed central muscular disorder – hypotonicity without significant lateralisation. She is still under control of neurologist.

## DISCUSSION

According to Rutherford (2002), despite improvements in perinatal care in the developed world, asphyxia remains a major cause of mortality, resulting in up to 25% of perinatal mortality and morbidity and giving rise to between 8 and 15% of all cases of cerebral palsy.

Changes in cerebral perfusion pressure most often reflected decreases in arterial blood pressure rather than increases in intracranial pressure.

Peculiarities of impact of oxidative stress on the Central Nervous System are: nervous tissue utilises extremely huge amount of oxygen and it creates conditions for creation mainly of superoxide radical; the white matter of the brain is the most vulnerable part in term newborn; polyunsaturated carboxylic acids are in the nervous tissue in very large quantities; nervous tissue has very high energy requirements and low anti-oxidative capacity; certain areas of the brain showed a high content of iron, which upon release from the binding proteins is strong catalyst for the formation of highly toxic reactive metabolites; density and placing of glutamate receptors in the developing brain contributes to vulnerability of certain brain areas during hypoxaemia and hypoxia; brain arteries react differently on hypoxia and hypoxia causes their dilatation.

Our patient was premature newborn with unknown history of prenatal asphyxia. We can only assume that combination of many risk factors (disease of mother, eclampsia, prematurity, severe prenatal hypotrophy; prenatal unknown severe brain ischaemia) could contribute to formation of brain infarction.

Ischemic stroke in our patient was presented clinically with generalised decreased muscular tonus but not with focal neurological signs such as hemiparesis as it was described by Akman *et al.* 2003, Estan & Hope, 1997.

## CONCLUSION

The central nervous system, and especially the white matter, is the most vulnerable area of the brain of the newborn. After exceeding the antioxidant capacity, oxidative stress belongs to the main factors involved in the pathogenesis of hypoxic-ischaemic encephalopathy.

Seizures as well as hypotonicity in the neonatal period may be the first symptoms of acute ischaemic cerebral infarction. The diagnosis in the acute phase can be established by the use of sonography (easily to perform; mobile; repeatable) for identifying cerebral oedema and intraventricular or parenchymal haemorrhage, computerized tomography (acute haemorrhage), and conventional magnetic resonance imaging (suitable for serial scanning; asphyxia) because of the high water content of the immature brain (Rutherford, 2002; Lani *et al.* 2011; Paonessa *et al.* 2010).

Detailed knowledge of the size of infarction can be measured and can help us to predict the prognosis (cor-

tical and white matter injury are associated with motor impairment; lesions of basal ganglia and of thalamus are associated with athetoid quadriplegia with poor neurodevelopmental outcome), but it will not change the prognosis of future development. The best way is to prevent prenatal foetal hypoxaemia and postnatal immediately after delivery with optimal neonatal management to decrease the spectrum of postasphyxiated consequences. All imaging techniques can help us to find pathological changes in the brain with respecting of different sensitivity, but most important is correct interpretation of the findings. Each patient requires multidisciplinary cooperation of physicians. Detailed prenatal investigation in preventing prenatal asphyxia and consequent complications is necessary.

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