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HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) IN TERM AND PRETERM INFANTS

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ABSTRACT

Hypoxic-ischemic syndrome (HIS) and Hypoxic-ischemic encephalopathy (HIE) are conditions that affect term and premature babies, with different pathophysiology and different brain disorders. HIE appears in 1-6 / 1000 live births and 26/1000 live births in developing countries. 15-20% die in the early neonatal period, while surviving babies have severe neurological impairment, including cerebral palsy, epilepsy, visual and hearing impairment, cognitive impairment, intellectual, behavioural, and social disorders. The hypoxic-ischemic event occurs before, during or after birth. The reasons may be related to the mother, the way of birth, the placenta, and the newborn. The criteria for diagnosis of HIE include a combination of perinatal factors, the need for resuscitation, standard neurological examinations, neurophysiological monitoring, neuroimaging methods and biochemical markers. The most effective treatment for HIE is hypothermia in combination with pharmacological therapy. HIE and HIS are problem that still persist in developing countries due to inadequate obstetric care, neonatal resuscitation, and hypothermia. Current and emerging research for HIE examines new markers for early recognition, treatment, and appropriate neuroprotection of high-risk term and premature infants.

Keywords: hypoxic-ischemic encephalopathy, Hypoxic-ischemic syndrome, term newborn, premature newborn

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) occurs in 1-6/1000 live births [1]. In developing countries, HIE occurs in 26/1000 live births [2]. The incidence of HIE is 1.5 per 1000 live births in developed countries and varies between 2.3-26.5 per 1000 live births in developing countries [3, 4]. The prevalence of hypoxic-ischemic encephalopathy (HIE) varies in the literature from 0.3 to 2 per 1000 term live births [5]. Frequency is two to nine per 1000 live births in developing countries [6]. Out of the total affected infants, 15–20% die in the early neonatal period, and 25%–30% of survivors have severe neurological impairment, including cerebral palsy, epilepsy, visual and hearing impairment, cognitive impairment, intellectual, behavioural, and social disorders [7]. From that aspect, this condition is one of the primary medical problems which significantly affects the patient, the family, and society.

Table 1. *Epidemiology for Hypoxic-ischemic encephalopathy*

Epidemiology for Hypoxic-ischemic encephalopathy	
Incidence	1.5 per 1000 live births in developed countries, 2.3-26.5 per 1000 live births in developing countries
Prevalence	0.3 to 2 per 1000 term live births
Frequency	2-9 per 1000 live births in developing countries

Hypoxic-ischemic syndrome (HIS) is a lack of oxygen due to hypoxic or ischemic injury occurring in the peripartum and/or intrapartum period in the newborn [8]. The hypoxic-ischemic event occurs before birth in 20% of newborns, 30% intrapartum, in 35% before and during birth, and only in 10% of newborns will the hypoxic-ischemic event develop after birth [9). In everyday clinical practice, there is a distinction between the terms hypoxia-ischemia and asphyxia. Hypoxemia is a low concentration of oxygen in the blood, hypoxia is reduced oxygenation of cells and organs, and ischemia is the reduced blood flow to tissues. Therefore, hypoxia and ischemia are often combined. In contrast, asphyxia is a disturbance in gas exchange and is characterized by anoxia and extreme hypercarbia [10]. Hypoxic-ischemic syndrome (HIS) affects the brain and other organs as well as organic systems: the heart (43–78%), lungs (71–86 %), kidneys (46–72 %), the liver (80–85 %), and the haematological system (32–54 %) [11]. Involvement of multiple organic systems within HIS leads to the development of multisystem organ failure (MOF).

HIE is a complex, multifactorial, evolving condition found in term and premature infants, which has a different pathophysiology and different affection of brain structures. Identifying, treating, neuroprotecting, and monitoring newborns with this condition in both groups is a challenge in everyday clinical practice. Recent data in regards to the manner in which complex mechanisms of HIE occur and potential predictive biomarkers of the HIE staging and further neuro-behavioural development are the focus of modern neonatology, perinatology, and neurophysiology.

Aetiology of hypoxic-ischemic syndrome (HIS)

Hypoxia-ischemia can develop before, during, or after birth. The reasons may arise from the mother, the way of birth, the placenta, and the newborn (Table 2). The most common causes are uterine rupture, placental abruption, prolapse of umbilical cord, a cardiovascular compromise with the mother, foetal-placental haemorrhage, foetal tachycardia with recurrent decelerations, and persistent minimal variables with recurrent decelerations [12].

Table 2: Risk factors for HIS

Risk Factors	
Birth	Spontaneous-vaginal, Caesarean section, Forceps, Vacuum extraction
Mother	uterine rupture, umbilical cord prolapse, compromised maternal cardiovascular system, infections, diabetes, hypertension, drugs, nicotine, alcohol
Placenta	placental abruption, placental insufficiency, foeto-placental haemorrhage
Newborn	pneumonia, sepsis, concomitant morbidities in premature infants-respiratory distress syndrome, necrotizing enterocolitis, bronchopulmonary dysplasia

Defining HIE in term and preterm infants

The classic definition of HIE in newborns proposed by the American College of Obstetricians and Gynaecologists includes the following criteria:

• Apgar score <5 in 5 min. and 10 min.

• -pH <7.0, and / or BE ≥-12 mmol / L, from the umbilical artery

• Acute brain injury detected by MRI (magnetic resonance imaging) or MRS (magnetic resonance spectroscopy) of the brain during the first week

• Multisystem organ failure in the first 48 hours [12].

The definition of HIE in preterm infants is still controversial. Below are listed the criteria for definite and probable HIE in preterm infants [13].

Definite HIE in premature infants (both criteria required)

• pH ≤7 and BE≥-12 mmol / L in foetal / umbilical / first neonatal blood sample (within 1 hour after birth).

• Neonatal encephalopathy – Sarnat staging - all criteria (except EEG) for newborns between 33 and 35 weeks of gestation, significant changes

in neurological examination and/or convulsions (for newborns less than 33 weeks of gestation).

Probable HIE in premature infants (any two criteria)

• pH 7.01–7.2 in a foetal / umbilical / first neonatal blood sample.

• Early multisystem organ failure (less than 48 hours)

• Preceding identifiable sentinel event-placental abruption, uterine rupture, umbilical cord prolapse, cardiotocograph abnormalities

• Prolonged need for assisted ventilation in the absence of respiratory disease/neuromuscular disorders (more than 72 hours).

• Prolonged metabolic acidosis (more than 24 hours).

• Specific change in MRI of the brain in the first week of life.

However, the definition of HIE is a matter of discussion and evolving controversy. Due to the significant differences in the stated criteria, their evaluation is needed. On the other hand, a precise definition of HIE staging is needed, which has not been published in our country so far.

Pathophysiological mechanisms of HIE in term and preterm infants

The pathophysiological and biochemical mechanisms in neonatal hypoxic-ischemic encephalopathy involves a cascade of reactions, where apoptosis or necrosis of nerve cells is the end result of brain damage. The pathophysiology of neonatal HIE includes three stages:

The first stage is the primary energy deficiency. This is the period of the first 6 hours of hypoxic-ischemic injury. It occurs in conditions of reduced blood flow through the placenta, leading to foetal hypoxia-ischaemia, acidosis, decreased myocardial contractility, decreased arterial blood pressure, and decreased cerebral blood flow [14]. Due to this, hypoxic-ischemic attack in the brain tissue, the anaerobic metabolism of glucose in the nerve cells is enhanced and adenosine triphosphate (ATP) is reduced. This leads to depletion of energy in the cell, disruption of the ion pump and transport of Na +, Ca ++, accumulation of lactate and free radicals, as well as mitochondrial dysfunction, nerve oedema and possible apoptosis.

The second stage is secondary energy deficiency. It occurs 6 to 72 hours after the hypoxic-ischemic event. Excited neurotransmitters (glutamate, GABA, aspatate) and free radicals continue to be released, mitochondrial dysfunction is more pronounced, and phosphorus reserves are depleted. Progression of this phase activates a number of cascading reactions, including inflammatory factors that emphasize the apoptosis or necrosis of nerve cells. Convulsions are expected to occur during this period [7].

The third stage is called as the stage of chronic inflammation. It occurs > 72 hours after the onset of the hypoxic-ischemic process and can last for days or months. Repair of damaged brain tissue can occur at this stage, where neurons and glial cells begin to multiply and regenerate, or when damage and degeneration of brain tissue continues by releasing harmful cytokines from microglia cells and astrocytes. This leads to damaged axonal growth, synaptogenesis, and neurogenesis [7,15].

Basal oxygen utilization is twice as high in newborns as in adults [16]. But in newborns with HIE, despite the hypoxic event, high doses of oxygen during and after resuscitation can lead to brain cell swelling and additional oxidative stress.

The outcome of HIE due to neuronal death results with a number of neurological lesions such as haemorrhage in brain structures, oedema, white and grey matter necrosis, infarction, white matter gliosis, atrophy, cysts, delayed myelination, ventriculomegaly, and hydrocephalus [17].

Studies of the pathophysiology of brain structures in term and preterm infants with HIE exhibit differences. The pathophysiology of HIE in premature infants is a set of complex and heterogeneous changes in the developing brain with a wide range of clinical manifestations. In premature infants there is still a highly active developmental process of dendritic / axonal growth, vasculogenesis, myelinogenesis and angiogenesis, deficiency of long-chain essential fatty acids, insufficient synthesis of certain growth factors, and increased exposure to adverse effects before, during and after delivery [17]. All of these changes in the premature infant make the developing brain vulnerable to injury from hypoxia-ischemia, inflammation, free radicals, and excitotoxic damage.

One of the significant differences of HIE in term and premature infants is in the histopathological features of the brain structures. In premature infants, the cerebral white matter is affected by the development of periventricular leukoma-

lacia (PVL), which results in the disruption of oligodendrocyte development and reduced myelination in the brain [18, 19]. In term infants, neuronal lesions are seen in the cerebral cortex, basal ganglia, and thalamus, where selective neuronal necrosis is predominant [20, 21].

HIE classification

The scale for HIE staging in term infants proposed by Sarnat & Sarnat (1976) is still widely used, despite numerous diagnostic modalities. According to this scale, based on the determination of consciousness, neuromuscular tone, primitive reflexes, autonomic function, convulsions, EEG changes, and duration, HIE is classified as mild, moderate, and severe encephalopathy [22, 23].

Diagnostic modalities

The diagnosis of HIE in term infants includes defined criteria in combination with perinatal factors such as acidosis, Apgar score, the need for resuscitation, and standard neurological examinations and neurodevelopmental monitoring [13, 24]. Recognizing HIE in premature infants is difficult. Neurological assessment may be performed by standard neurological examination in neonates at 33 to 35 weeks of gestation, but at <33 weeks of gestation clinical features may be masked by physiological immaturity [13]. There are various tools for early detection of HIE, but none of them is completely specific and sensitive.

Magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (1H-MRS) are imaging methods for visualizing brain lesions in HIE, including white matter changes, PLV, cysts, ventriculomegaly, delayed myelination [25]. MRS measures local biochemical changes in the brain and is useful for assessing metabolic changes associated with brain development and injury [13]. These methods offer excellent opportunities to predict the outcome and neurological development in neonates with HIE [26]. In meta-analyses it is proven that posterior limb of the internal capsule (PLIC) abnormalities on MRI, apparent diffusion coefficient (ADC) values of the thalamus, and MRS are most predictive of neurodevelopmental outcomes. [27]

Amplitude electroencephalography (aEEG) and electroencephalography (EEG) are powerful tools for diagnosing and predicting the neurological outcome of newborns with HIE. Meta-analysis shows that aEEG at 72 h and EEG at 24 and 72 h after birth were superior to aEEG at 6 h and EEG at 48 h [27]. In preterm infants, interpretation of the EEG is more complex due to the development of the developing brain. Findings of increased discontinuity, decreased rapid frequency activity, and decreased amplitudes in the first and second postnatal days of infants at 27 to 32 weeks of gestation indicate a high predictive potential for neurological development. Also, aEEG in the first 6 hours of birth in newborns from 34–36 weeks of gestation is important in neurodevelopmental processes [28, 29].

Near-infrared spectroscopy (NIRS) is useful for the analysis of tissue oxygenation indices and regional oxygen saturation in the brain in various pathological processes. NIRS provides important data on metabolic dynamics in different regions of the brain and has prognostic significance for HIE in term infants. The criteria for the use of NIRS in preterm infants with HIE are not fully defined [13].

Biomarkers for early detection and prediction of HIE

In neonatal hypoxic-ischemic encephalopathy, the greatest challenge is to predict, detect, and evaluate this condition in the newborn. Using the known clinical criteria, about 20 % of newborns with poor outcome are missed [30]. Today's research focuses on discovering specific and highly sensitive biological and physiological markers for early detection, monitoring and evaluation of HIE at an early stage, where routine neuroimaging tools are not yet able to respond. There are certain studies which establish a correlation between HIE and heart rate variability (HRV) as a potential biomarker for the severity of neonatal HIE during the acute phase of injury [31]. Most of the studied biomarkers have a protein structure and are released when nerve tissue is locally injured in the cerebrospinal fluid and in the circulation. In selecting the most suitable biomarkers for HIE, several factors are important: the time of sampling, the type of biological fluid, the clinical phenotype and the biochemical structure of the biomarker, as well as its/their ability to predict. Studies have evaluated the predictive values of UCH IL-1, IL-6, IL-16, activin A, LDH, GFAP, lactate, S100B, NSE, microRNA [32, 33]. This list is long and new biomarkers are explored daily which, in the future, will offer early, rapid, and reliable iden-

tification of neonates with HIE. Thus we will be able to start neuroprotective interventions early.

Therapy and neuroprotection

An accepted therapeutic modality for HIE is the use of hypothermia. Hypothermia is performed according to standard protocols for the selective cooling of the head. This includes "head cooling" or the cooling of the whole body, "body cooling'". The results of recent clinical trials suggest that both methods have a neuroprotective effect [34]. According to some meta-analyses, whole body cooling is more applicable and effective due to the systemic effect of cooling almost all parts of the brain, while selective head cooling affects only the cortical part of the brain [35]. The general standard for starting treatment with hypothermia is the so-called "therapeutic window", the first 6 hours after birth, when energy metabolism is still not reduced. New research confirms that hypothermia reduces and prevents the formation of free radicals and NO much earlier, even within 30 minutes of birth [9]. The exact mechanism of neuroprotection of hypothermia is not clear enough, but it is associated with reduced glutamate release, decreased metabolism and energy consumption in brain tissue, reduced neuronal acidosis and promoted protein synthesis, decreased leukotriene synthesis, reduction of blood-brain barrier damage and brain oedema, free radical inhibition, inhibition of cell apoptosis and/or inhibition of free radical generation, and lipid peroxide reaction [7]. Neurodevelopmental monitoring of children up to 7 years of age has shown significant decrease in incidence of cerebral palsy, as opposed to children without hypothermia [36]. Certain meta-analyses indicate that therapeutic hypothermia reduces mortality and neurodevelopmental delays compared to usual care. Whole body hypothermia is preferable for infants with HIE, because it reduces the risk of morbidity as well as neurodevelopmental delays [37].

The use of hypothermia in preterm infants with HIE is limited. Under hypothermia, the haemoglobin dissociation curve shifts to the left and reduces the tissue oxygen, impairing oxygenation in preterm infants with severe respiratory morbidity [10].

The most effective treatment for HIE would be hypothermia in combination with pharmacological therapy that would mutually affect the destructive processes caused by hypoxic-ischemic attack. The aim is to discover the optimal combination of a pharmaceutical preparation that will complement the hypothermic therapy.

Clinical trials have shown that in neonates with moderate/severe HIE, melatonin therapy in combination with mild hypothermia reduces oxidative stress, improves survival and neurological development at 6 months of age [38].

Randomized studies with moderate hypothermia and the use of high doses of recombinant erythropoietin in neonates with HIE show a reduction in MRI-confirmed brain changes and improvement in motor function in the first year [39, 40]. Erythropoietin promotes neuronal differentiation and regeneration in HIE. It may inhibit apoptosis, regulate the inflammatory response and antioxidant damage, and thus promote vascular regeneration and improve microcirculation [7].

Reduction of brain damage after hypoxic-ischemic attack by pharmacological neuroprotection alone is not yet available.

Research for use of cannabinoids and azithromycin as possible pharmacotherapy for HIE are in the experimental phase. Cannabinoids have anti-neurotoxic and anti-inflammatory properties and protect the brain after neonatal hypoxia-ischemia (41). Azithromycin is a macrolide antibiotic that improves neurological function, probably based on its anti-inflammatory properties [42].

Recent clinical studies in regenerative medicine have focused on the study of embryonic stem cells as a possible treatment for brain damage caused by hypoxic-ischemic attacks. Embryonic stem cells have the potential to differentiate into haematopoietic, nerve, or mesenchymal stem cells. Of all of the above, mesenchymal stem cells are studied in clinical trials and treatment is possible due to its neuro-regenerative and important immune-modulating effects [43,44]. Mesenchymal stem cells stimulate the formation of new brain cells by paracrine action rather than the transformation into neuronal tissue [45, 46].

CONCLUSION

HIE is a global problem. Developing countries are in a more difficult position as they lack adequate and modern obstetric care, proper and timely neonatal resuscitation and hypothermia as possible therapy. By defining and discovering

effective, affordable and inexpensive measures and markers, this condition in newborns can be identified early and treated appropriately. New bio- and physiological markers, individually or in combination, are in focus of modern research for HIE, which will allow timely recognition, treatment and appropriate neuroprotection of high-risk term and premature infants.

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Резиме

ХИПОКСИЧНО-ИСХЕМИЧНА ЕНЦЕФАЛОПАТИЈА (HIE) КАЈ ДОНОСЕНИ И ПРЕМАТУРНИ НОВОРОДЕНЧИЊА

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Хипоксично-исхемичниот синдром (HIS) и хипоксично-исхемичната енцефалопатија (HIE) се состојби што се среќаваат кај доносените и предвремено родените бебиња, со различни патофизиолошки механизми и различно мозочно нарушување. HIE се појавува кај 1–6/1000 живородени, а во земјите во развој кај 26/1000 живородени деца. 15–20 % од новорденчињата со HIE умираат во раниот неонатален период, додека преживеаните имаат тешки невролошки секвели, вклучувајќи церебрална парализа, епилепсија, оштетување на видот и на слухот, когнитивни, интелектуални, бихејвиорални и социјални нарушувања. Хипоксично-исхемичниот процес се јавува пред, за време или по раѓањето. Причините може да се поврзани со мајката, начинот на раѓање, плацентата и новороденчето. Критериумите за дијагноза на HIE вклучуваат комбинација на перинатални фактори, потреба од реанимација, стандардни невролошки прегледи, неврофизиолошки мониторинг, неуроимиџинг и биохемиски маркери. Најефикасен третман за HIE е хипотермијата во комбинација со фармаколошка терапија. HIE и HIS се проблеми што сè уште опстојуваат во земјите во развој поради несоодветната акушерска нега, несоодветната неонатална примарна реанимација и хипотермија. Актуелните и нови истражувања за HIE ги испитуваат новите маркери за рано препознавање, третманот и соодветната невропротекција на високоризичните доносени и предвремено родени новороденчиња.

Клучни зборови: хипоксично-исхемичниот синдром, хипоксично-исхемичната енцефалопатија, доносени новороденчиња, прематурни новороденчиња