Hypoxic-ischemic encephalopathy

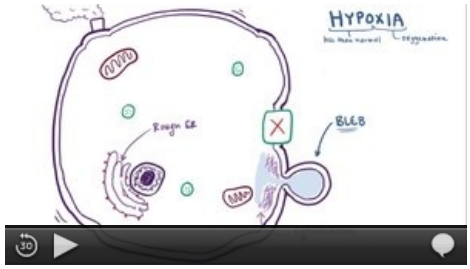
Hypoxic-ischemic encephalopathy (HIE) is a clinical-pathological entity that arises as a result of diffuse hypoxic-ischemic damage to the central nervous system in a full-term newborn. The most common cause is perinatal asphyxia. Periventricular leukomalacia develops in premature newborns under these conditions.

The extent of central nervous system damage depends on the severity of HIE. Mortality rates of 25-50% are reported for severe forms of HIE. Death usually occurs within the first week of life due to multi-organ failure. About 80% of children with severe HIE who survive have serious complications, including cerebral palsy, psychomotor retardation, deafness, blindness, epilepsy. In indicated cases, the consequences of HIE can be mitigated using controlled hypothermia.[1]

Pathophysiology

Asphyxia → cytotoxic cell damage → cytotoxic edema (reversible changes) → vasogenic edema (irreversible changes).

Note: Brain edema that occurs during HIE can progress in the form of cytotoxic edema even if it is possible to quickly stabilize the cerebral perfusion pressure.



Hypoxia (video).

1. **Early stage** - the stage of primary loss of neurons by necrosis
   - The consequence of the collapse of the cell's energy metabolism due to membrane instability and dysfunction, ion imbalances, the influence of NO, oxygen radicals, nitrites, excitotoxicity of amino acids, activation of inflammatory cells, cell necrosis, the possibility of starting apoptosis play a significant role.
2. **Late phase** – the phase of secondary loss of neurons by apoptosis (2-12 hours after the acute insult).
   - Consequence of apoptosis and the response of activated microglia.[2]

HIE results from cerebral hypoxia and ischemia caused by systemic hypoxemia and reduced cerebral blood flow. In asphyxia, as a result of hypoxia and hypercapnia, the blood flow through the brain increases with the simultaneous redistribution of cardiac output to essential organs (brain, heart, adrenal glands). Adrenaline secretion increases and thus blood pressure rises. In adults, cerebral autoregulation maintains constant cerebral blood flow despite fluctuations in systemic blood pressure (60–100 mm Hg). In newborns, this autoregulation seems to work only when the systemic BP fluctuates slightly. In a neonate affected by acute asphyxia, after exhaustion of early compensatory mechanisms, cerebral blood flow becomes dependent on systemic BP. As BP falls, cerebral blood flow falls below a critical value and brain damage develops due to reduced blood supply and lack of oxygen. An energy failure occurs intracellularly. The temperature of the brain decreases and neurotransmitters (GABA) are released. These changes reduce oxygen demands in an effort to minimize the impact of asphyxiation. The extent of final neuronal damage depends on the duration and severity of the initial insult as well as on reperfusion injury and apoptosis.[1]

Activation of excitatory amino acid (EAA) receptors plays a critical role in the pathogenesis of HIE. During brain hypoxia/ischemia, the uptake of glutamate (the main excitatory neurotransmitter) is impaired, resulting in high synaptic levels of glutamate and increased activation of EAA receptors (NMDA, AMPA, kainate receptors). These receptors are permeable to Ca2+ and Na+. Accumulation of these ions with concomitant failure of the energy-demanding Na+/K+ATPase leads to rapid cytotoxic edema and cell death (necrosis). Increased intracellular calcium leads to programmed cell death. Developing oligodendroglia are highly susceptible to hypoxia/ischemia, especially excitotoxicity and free radical damage. This white matter damage may underlie learning and memory impairments in children with HIE.[1]

After hypoxia/ischemia, intracellular calcium concentration subsequently rises due to activation of NMDA receptors, release of calcium from intracellular stores (mitochondria and endoplasmic reticulum) and due to impaired excretion of calcium from the cell. An increased concentration of intracellular calcium leads to the activation of phospholipases, endonucleases, proteases leading to apoptosis, and in some neurons also NO-synthetase. Activation of proteases and endonucleases damages the cytoskeleton and DNA.

During the reperfusion period, the production of free radicals increases due to the activation of cyclooxygenase, xanthine oxidase and lipoxygenase. Newborns have an immature defense against antioxidants. Free radicals can lead to lipid peroxidation, DNA and protein damage, and can trigger apoptosis. Free radicals can form highly toxic peroxynitrite with NO. Activation of NMDA receptors transiently increases NO concentrations in the initial phase of hypoxia. As a result of the inflammatory response to cerebral ischemia, NO production increases (the second surge) - detectable up to 4-7 days after the insult.

Inflammatory mediators (cytokines – e.g. interleukin 1b – and chemokines) are also involved in brain damage.

6–24 hours after the initial damage, a new phase of neuronal damage occurs ("delayed phase of neuronal damage") characterized by mitochondrial dysfunction and the initiation of the apoptotic cascade.

Other factors that influence outcome are IUGR, pre-existing brain pathology and brain malformations, frequency and severity of seizures.[1]

Clinical image

- We evaluate clinical symptomatology according to classification schemes - most often Sarnat and Sarnatová or Levene et al.[2]

Sarnat staging

I. grade (mild HIE)

- Hyperexcitability, hyperreflexia, hypertonia, prolonged wakefulness, pupil normal, possibly mydriasis, Moro with low equipment threshold, no convulsions present.
- Prognosis: symptomatology resolves within 1–3 days, ICU monitoring is appropriate, but most children do not require further neurological monitoring.[2]

II. grade (moderately severe HIE)

- Reduced reflexes (sucking, grasping, Moro), hypotonia, lethargy, apathy alternates with irritability, reduced spontaneous movement, or pathological movements: "pedalling" = pedaling a bicycle, "boxing" = boxing, thumbs clenched into fists, bradycardia, central apnea, suction disorders, miosis, subtle convulsions. Prognosis: symptoms usually appear immediately after birth, last for 3-7 days, ICU monitoring is appropriate, 15-30% of children have long-term consequences, usually children where the initial symptomatology persists for more than 1 week.[2]

III. grade (severe HIE)

- Stupor or coma, gradual development of decerebrate rigidity, minimal spontaneous mobility, absence of reactions to nociceptive stimulus, hyporeflexia/areflexia, areactive pupils, central apnea, convulsions difficult to control pharmacologically.
- Prognosis: in the first 12 hours there is a slight improvement in consciousness, but this is followed by further deterioration up to brain death, 50% of newborns have permanent effects, 50% of newborns die.[2]

Clinical degrees of perinatal hypoxic-ischemic brain damage according to Sarnat staging[1]

	Grade I	Grade II	Grade III
State of consciousness	irritant	lethargic or numb	stuporous
Neuromuscular control			
Muscle tone	normal	mild hypotonia	significant hypotonia
Posture	slight distal flexion	significant distal flexion	intermittent decerebration
Tendon-muscular (tension) reflexes	increased	increased	reduced or disappeared
Segmental myoclonus	present	present	missing
More complex (complex) reflexes			
Sucking reflex	weak	reduced or disappeared	missing
Moro's	strong; low threshold	weak; incomplete; high threshold	missing
Oculovestibular	normal	increased	reduced or disappeared
Tonic nuchal	weak	strong	missing
Autonomous function	generalized sympathetic	generalized parasympathetic	both systems reduced
Pupils	mydriasis	miosis	changeable; often unequal; poor reaction to light
Heart action	tachycardia	bradycardia	changeable

Diagnostics - imaging methods and other examinations

- magnetic resonance imaging of the brain - suitable for diagnosis, monitoring the development of the disability and determining the prognosis;
- brain ultrasound – lower sensitivity;
- electroencephalography – to assess the extent of the impairment and diagnosis of subclinical convulsions;
- hearing and vision examination.[1]

Pathological anatomy

The clinical-pathological picture depends on the severity of the insult, the time elapsed since the insult and whether the brain was affected by simple asphyxia or a combination of asphyxia and ischemia.

- asphyxia → brain edema, selective neuronal necrosis, subcortical gray matter lesions;
- asphyxia + ischemia → "watershed" ischemia (periventricular leukomalacia - cortical and subcortical leukomalacia), focal ischemia (focal lesions in the basin of the a. cerebri anterior, a. cerebri media and parasagittal lesions).[2]

Hypoxic-ischemic damage to the cerebral cortex – *locus minoris resistentiae*:

- lower parts of sulci;
- III. – V. layer.[3]

Hypoxic-ischemic damage of white matter – *periventricular locus minoris resistentiae*:

- mild regression (edema, swelling of astrocytes);
- partial necrosis;
- complete necrosis (leukomalacia).[3]

Late consequences of hypoxic-ischemic encephalopathy:

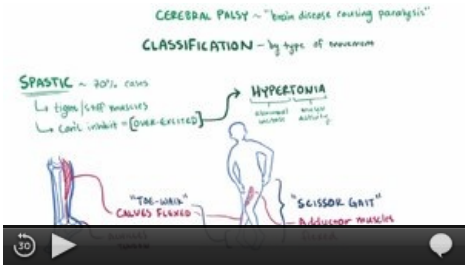
- minimal brain lesions;
- cortical dysgenesis;
- ulegyria (originally normally formed convolutions, which were secondarily irregularly bent and narrowed; convolutions are rigid, extinct neurons have been replaced by glia);
- pseudocysts – multifocal cystic encephalopathy (cortex and white matter are permeated by a number of cavities separated by gliofibrous septa);
- status mramoratus (marbled and reduced striatum or thalamus; arises as a result of neuronal loss, gliosis and hypermyelination).[3][4]

Therapy

- Comprehensive measures as in asphyxia/hypoxia: ensure ventilation and perfusion with timely cardiopulmonary resuscitation, stabilization of the patient, minimal handling of the patient.[2]
- Treatment of all organ failures – circulatory, ventilation, kidney, liver and coagulopathy.
- Maintaining the balance of the internal environment (normoglycemia, normocalcemia).
- Treatment of convulsions.
- Thermal management.
- Controlled hypothermia – start within 6 hours of insult, body temperature maintained at 34±0.5°C for 72 hours.

Prognosis

Sources



Cerebral palsy (video).

Related articles

- Cardiopulmonary resuscitation of the newborn
- Neonatal hypoxia
- Diagnosis of fetal condition during pregnancy and delivery • Intrapartum fetal monitoring • Fetal hypoxia

External links

- Doporučený postup ČNeoS (2019): ŘÍZENÁ HYPOTERMIE V LÉČBĚ HYPOXICKO – ISCHEMICKÉ ENCEFALOPATIE (http://www.neonatology.cz/upload/www.neonatology.cz/Legislativa/Postupy/hie-a-rizena-hypotermie-revize-doporuceneho-postupu-27052019.pdf)

References

1. ZANELLI, Santina A. *Hypoxic-Ischemic Encephalopathy* [online]. The last revision 2011-12-15, [cit. 2012-04-30]. <https://emedicine.medscape.com/article/973501-overview>.
2. HAVRÁNEK, Jiří: *Asfyxie x HIE*.
3. Patologicko-anatomický ústav FN Brno - LF MU. *Hypoxicko-ischemická encefalopatie novorozenců* [online]. [cit. 2012-05-01]. <http://www.med.muni.cz/patanat/encefalopatie.html>.
4. Ústav patologie, Masarykova univerzita v Brně. *Patologie novorozence : Hypoxicko-ischemická encefalopatie (HIE)* [online]. [cit. 2012-05-01]. <https://atlases.muni.cz/atlases/novo/atl_cz/main+novorozenec+novorasfyxcas.html>.