HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN ADULT

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Abstract: *Hypoxic-ischemic encephalopathy (HIE), is one of the most frequent and dramatic urgency found in neurological brain diseases of adults. This is a neuro-vascular and neuro-metabolic syndrome, caused by a shortage of supply of oxygen and glucose or their metabolism in the brain. HIE results from a global hypoperfusion or oxygenation deficiency rather than from infarction in a specific vascular cerebral territory. In adults, common etiologies include hypotension, cardiac arrest followed by succesful resuscitation, and carbon monoxide poisoning. The prognosis is favorable with recovery in case of mild or moderate hypoxia of short duration. Prognosis is unfavorable in hypoxic-ischaemic encephalopathy after severe damage.*

Cuvinte cheie: *hipoxie cerebrală, ischemie cerebrală difuză, leziuni tisulare cerebrale, sindroame neurologice posthipoxice*

Rezumat: *Encefalopatia hipoxic-ischemica este unul din cele mai frecvente şi dramatice afecţiuni cerebrale întâlnite în urgenţa neurologică a adultului. Este un sindrom neuro-vascular şi neuro-metabolic, determinat de un deficit al aportului de oxigen si glucoză sau de metabolizare a acestora la nivelul creierului. HIE rezultă mai degrabă dintr-un deficit global de hipoperfuzie sau oxigenare decât dintr-un infarct într-un teritoriu vascular cerebral specific. La adulţi cauzele comune sunt hipotensiunea, stopul cardio-respirator urmat de resuscitare eficientă, intoxicarea cu monoxid de carbon. În cazul unei hipoxii uşoare sau moderate, de scurtă durată, prognosticul este favorabil. Prognosticul este nefavorabil în encefalopatia hipoxic-ishemică după leziuni cerebrale severe*

Cerebral hypoxia can be classified according to severity and location, in:

- **diffuse cerebral hypoxia**: mild to moderate impairment of global brain function caused by low levels of oxygen in the blood.
- **focal cerebral ischemia**: a localized and temporary reduction of brain tissue oxygenation. Neuronal damage is usually reversible. Ex: TIA.
- **cerebral infarction:** a long-term blockage of blood flow to a region of the brain. Significant irreversible damage occurring in the area after obstruction.
- **global cerebral ischemia**: a complete and diffuse stop of blood flow to the brain (eg. severe systemic hypotension in shock, cardio-respiratory arrest). (1)

Depending on the cause of the reduction of oxygen to the brain, cerebral hypoxia may be: hypoxic, hypemic / anaemic, ischemic and hystotoxic. (see Table no. 1) (2)

Neurophysiology

The brain needs 3.3 ml O2/100g/min and 8 mg glucose/100g/min under basal cerebral condition at a blood flow to an average of 55 ml/100g/min (ie 750 ml / min) representing 15 -20% of total cardiac output at rest. Blood flow of gray substance (cortex) is 4-5 times higher (70-80 ml/100g/min) than that of white matter (15-20 ml/100g/min). In people over 60 years, cerebral blood flow is 30-40 ml/100g/min.(2)

Neurophysiopathology

In case of reduction of O2 concentration in the blood, the body respond to compensate by redirecting systemic blood flow and increasing cerebral blood flow, up to 2 times normal. If this increasing is sufficient to meet the brain needs of O2, then symptoms characteristic of hypo / anoxia of brain does not appear. If the adaptive response of O2 deficit is not corrected, the symptoms begin to appear. (3), (4)

When brain hypoxia appear, brain tissue suffering is not equal in all territories, newer developed phylogenetically formations are the most sensitive. By microelectrodes studies has been showed that signs of distress tissue in different areas (demonstrated by lack of neuronal electrical activity) is installing in variable periods of time after the onset of hypoxia, namely:(5)

- at 10-12 seconds for the cortex, Ammon's horn, Purkinje cells
- at 25-27 seconds for caudate nucleus
- At 35-37 seconds ventral nucleus of the thalamus
- At 30-40 seconds for bulbar gray substance

The most common causes of acute cerebral hypoxia is the dropping of cerebral perfusion (global cerebral ischemia) caused by cardio-respiratory arrest and severe hypotension (haemodynamic shock). Sustained severe hypoglycaemia, sustained seizures (status epilepticus) over 1-2 hours may also cause permanent brain damage. Global cerebral ischemia is more aggressive, because in addition to the energy shortage is leading to accumulation of lactic acid and free radicals, which are removed during normal blood flow conditions as they accumulate.

Shortage of energy substrate (O2, glucose) in the brain has these negative effects: impaired Na-K pump results in prolonged neuronal depolarisation and release of excess glutamate from the synapses. It then activates NMDA and AMPA receptors, leading to a massive influx of Ca in neurons with consequent activation of catabolic enzymes and NO production and formation of free radicals. They cause irreversible neuronal damage and neuronal death. Therefore

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modalities of seeking to neutralize the action of glutamate are therapeutic measures underlying the neuroprotective strategies. (6)

Table no. 1. Classification of cerebral hypoxia according to the causes of reduction of oxygen concentration in the brain

Type	Circumstances	Causes
Hypoxic hypoxia	reduction of oxygen concentration in the atmosphere, acute respiratory disease	• high altitude • Breathing ineffective (ALS, Guillain-Barre sdr) • obstruction of air routes • asthma
Hypemic/ anaemic Hypoxia	reduced capacity of anaemic blood (Hb) in oxygen fixation	• Reducing the number of red blood cells, the Hb (anaemia) • abnormal Hb (sickle cell) • CO intoxication
Ischemic hypoxia	Stenosys / obstruction of cerebral circulation and decreased bloodflow to the brain	• Stroke • myocardial infarction • shock
Hystotoxic hypoxia	O2 is in normal concentration in blood, but can not be metabolized in tissues	• metabolic intoxication (cyanide)

Incomplete combustion of glucose in hypoxia leads to the formation of lactate and H which contributes to the development of cerebral edema (initially cytotoxic and then interstitial) and to intracranial hypertension syndrome (ICH). Damage to small vessels (vascular endothelium) leads to accumulation in the interstitial space of fatty acids, lactic acid, electrolytes, arachidonic acid (proinflamatory and chemotactic function). These metabolites of plasma origin and local perivascular inflammation do not appear in conditions of complete ischemia (vascular obstruction), but occur at the stage of reperfusion (the so-called *injury of reperfusion)*.(7)

Symptoms and signs of cerebral hypoxia:

Depending on the duration of cerebral hypoxia the following clinical events are observed (see Table no. 2): (8), (9)

Tabel no. 2. Clinical signs which occur depending on the duration of cerebral hypoxia

Duration of hypoxia	Clinical signs
Up to 1 minute	Unconsciousness, convulsions, miosis, abolished pupillary reflex
After 2 minutes	Mydriasis, the abolition of corneal reflex
After 5 minutes	Cerebral cortex suffering irreversible damage
After 15 minutes	Irreversible damage at brain stem and the spinal cord

Clinical applications

In one patient with a short episode of global cerebral ischemia (syncope), within seconds, electric energy deficit causes the decrease of the neural electrical activity and the patient loses consciousness.

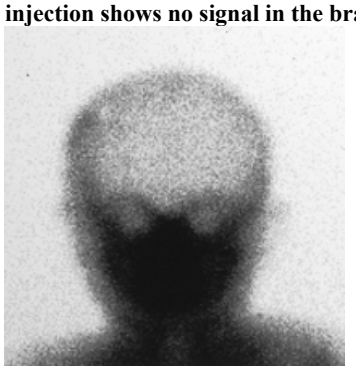
Neurons and glial cells are viable, and if circulation is restored promptly, the patient regains consciousness. If ischaemia lasts longer, at first is compromised the integrity of neuronal membranes and then the neuronal metabolism resulting in neuronal cell death by apoptosis. 4-5 minutes of ischaemia may irreversibly damage cortical pyramidal cells (layers 3,5,6) and hippocampus (CA1), neurons in the corpus striated and Purkinje cells. Ischaemia lasting longer leads to irreversible damage in thalamus and brain stem. Spinal cord remain unaffected for longer periods, even after the rest of the CNS was severely injured. An explanation of this selective vulnerability is that neurons more susceptible are the ones that most likely produce more glutamate.

Severe hypoxia which harms the cortex, basal nuclei and brain stem is resulting in brain death.

This is a clinical and paraclinical terminal condition characterized by a lack of response to external stimuli, absence of brain stem reflexes, isoelectric EEG and absence of brain perfusion. Lack of cerebral perfusion is due to blocked arterioles (by endothelial edema = no-reflow phenomenon) and because of cerebral edema. In this case the differential diagnosis is made with deep general anesthesia, various poisoning, hypothermia, conditions that can lead to coma and isoelectric EEG.

If a patient who is in brain death is artificially ventilated for a longer period, the brain goes through a process of enzymatic autolysis (liquefaction by autolysis), which was called by the term of *respiratory brain*. It has been replaced with the term of *nonperfused brain.*

Figure no. 1. Appearance of nonperfused brain. Radionuclide injection shows no signal in the brain



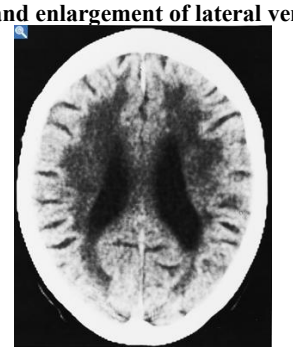
Diffuse cortical neuronal loss, thalamic or combined (but with unaffected brainstem) leads to severe dementia or persistent vegetative state (characterized by loss of cognitive functions and emotions but with preservation of sleep-wake cycle, autonomic functions and spontaneous breathing).

In some patients with epilepsy (after repeated episodes of generalized seizures) or in patients with short episodes of cardio-respiratory arrest, lesions with neuronal loss in hippocampus and bilateral gliosis (hippocampus sclerosis) occur, which can lead to Korsakoff amnesia, characterized by a deficit in establishing new information (anterograde/ posttraumatic amnesia), and a less severe deficit in evoking old memories (retrograde amnesia).

White matter is rarely affected in cases of acute cerebral hypoperfusion. An exception is the case of acute CO intoxication in which after a few weeks after injury appears an autoimmune response in subcortical myelin layers. In situations of chronic cerebral hypoperfusion occurs a subcortical axonal demyelination.

On CT or MRI examination that demyelination is called leucoarayosis (from Gr: *leucos* = white ,*araios*= least dense, thin). It is associated with small vessel disease (in chronic hypertension, cerebral amyloid angiopathy, CADASIL desease, Binswanger's desease) and lead to dementia. White matter pathology is usually associated with subcortical incomplete infarctions and hemorrhages.

Fig no. 2. CT in a patient with Binswanger's disease: hypodense diffuse white matter around the ventricles (leucoarayosis) and enlargement of lateral ventricles.



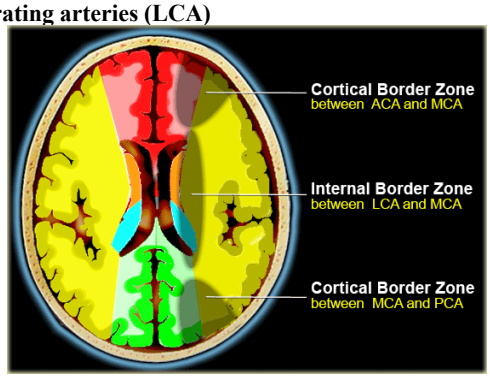
Severe hypoxia may be well tolerated if it occurs progressively. Some patients with severe chronic lung disease does not show signs of impairment of consciousness even when arterial oxygen partial pressure is 30 mmHg. This value, when suddenly occurs to a healthy individual, causes coma. (8), (9), (10)

Posthypoxic neurological syndromes

They are: coma or persistent vegetative state, dementia, extrapyramidal syndrome (parkinsonian) with cognitive deficit (in CO poisoning), coreoathetosis, cerebellar ataxia, myoclonus, Korsakoff's disease.

If injuries are caused by global ischaemic hypoperfusion, the patient may present specific manifestations of watershed strokes (border zone): visual agnosia (Balint's syndrome or cortical blindness) when the lesion is between the territories of MCA and PCA, proximal upper limb motor deficit, sometimes to the leg when damage is located between MCA and ACA territories.

Fig no. 3. Different border zone strokes, cortical or deep, between the territories of arteries MCA, PCA, ACA and penetrating arteries (LCA)



Balint's syndrome is characterized by a parieto-occipital bilateral ischaemia, manifested by optic ataxia, oculo-motor apraxia and psychic paralysis of gaze.

Seizures can occur, often resistant to therapy, and of which myoclonus is common and shows a sign of seriousness. (8), (9)

Late anoxic encephalopathy

It is a relatively rare phenomenon in which the initial improvement, apparently complete, is followed by a variable period (between 1-4 weeks) of a relapse: apathy, confusion, irritability, occasional agitation or mania. Most subjects survive the phenomenon, but some remain with severe mental and motor disorders and in some cases death occurs. (8),(9)

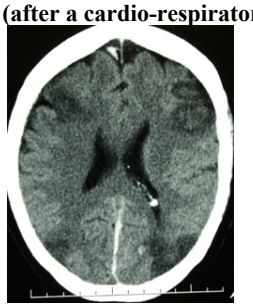
Prognostic

Improving in case of mild or moderate short lasting global hypoxia (seconds), with some minor temporary effects. Focal signs apear in case of localized persistent ischaemia. Could follow a state of permanent dementia or a state of superficial coma (or permanent vegetative state).

Prolonged severe hypoxia leads to irreversible brain damage, as evidenced by: the presence of fixed mydriasis and paralysis of eye movements for 24-48 hours, GCS less than 7. This is diagnosed after the exclusion of other causes (intoxication, deep anesthesia, hypothermia).

Family impact is significant. They have frequently idealized perspectives (often inspired by the media) making it difficult to accept unfavorable prognosis. Therapeutic decision is often influenced by complex ethical situations (brain death, organ transplants).(8),(9)

Fig no. 4. border zone infarction (watershed) between cortical territories ACA, MCA and PCA in a patient with Balint's syndrome (after a cardio-respiratory arrest).



Therapy

It is made by urgent initiation of the following measures: removing the cause of hypoxia, recovery of cardiac and pulmonary function (by resuscitation, respiratory support, defibrillation, pacemakers), oxygen (hyperbaric O2 in CO intoxication), blood glucose and blood pressure control, therapy and prevention of aggravation of focal cerebral ischemic injury, induction of controlled hypothermia - the cooling blankets (core T at 33 ° C) for 2 hours, immediately after resuscitation (is reducing cerebral metabolic needs and may improve prognosis).

To be given corticosteroids, prevention of cerebral edema, anticonvulsants (midazolam or neuromuscular blockers in cases of resistance to therapy, anesthesia). Myoclonus can be treated with clonazepam 8.12 mg / day. Fever and chills are treated with antipyretic, low body temperature from outside (cold applications) or neuromuscular blockade. (8),(9),(11),(12)

CONCLUSIONS

After those presented can be said of hypoxic-ischemic encephalopathy in adults that is caused by a shortage of supply of oxygen and glucose or their metabolism in the brain. The most common causes are cardio-respiratory arrest and haemodynamic shock. Brain tissue lesions are variable and depend on the duration and severity of the hypoxic / ischaemic phenomenon (from reversible to irreversible) and different degrees of sensitivity to hypoxia of different brain areas. Clinical manifestations vary depending on the duration, severity and localisation of the phenomenon and the causes of reduction of O2 concentration in the blood.

It is made a clinical diagnosis (based on history, signs and symptoms) and laboratory diagnosis (based on laboratory investigations, imaging and neurophysiological data).

Posthypoxic neurological syndromes can include: coma or persistent vegetative state, dementia, extrapyramidal syndrome with cognitive deficit (in CO poisoning), coreoathetosis, cerebellar ataxia, myoclonus, Korsakoff amnesia. Late postanoxic encephalopathy phenomenon may also be present.

The prognosis is favorable with recovery in case of mild or moderate hypoxia of short duration. Prognosis is unfavorable in hypoxic-ischaemic encephalopathy after severe damage.

Hipoxic-ischemic encephalopathy requires the establishment of therapeutic measures as early as possible (in the ambulance, in pre-hospital, in the emergency room, the ICU unit) which aims: removing the cause of hypoxia; resuscitation, hemodynamic, metabolic and electrolyte balance, oxygen (with respiratory support), focal brain lesion therapy, prevention of cerebral edema, anticonvulsants, antipyretics.

It is very important the effective collaboration between physicians of different specialties which are coming in contact with the patient with hypoxic-ischemic encephalopathy and efficent resolution of ethical issues (brain death diagnosis, the possibility of organ transplantation).

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