Hypoxic-ischemic syndrome

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Abstract

Objective: to review the literature on the hypoxic-ischemic syndrome, emphasizing its physiopathology, clinical manifestations, and treatment.

Sources: electronic search in the Medline and LILACS databases, with selection of the most relevant articles.

Summary of the findings: the hypoxic-ischemic syndrome is a multisystem disease with generalized manifestations. The physiopathology is based on hypoxic-ischemic brain injury and reperfusion with cellular injury caused by failure of ATP production secondary to ischemia, and overproduction of oxidative substances caused by reperfusion. Neurological, cardiovascular, respiratory, metabolic, gastrointestinal, renal, and hematological manifestations are frequent. Multisystem clinical management is complex; the neuroprotective approach is still experimental; and the prognosis is not good for those patients with severe hypoxic-ischemic encephalopathy.

Conclusions: the management of the hypoxic-ischemic syndrome is a great challenge to pediatricians, since treatment requires multisystem intervention.


Definition

Hypoxic-ischemic syndrome (HIS) occurs in the presence of significant tissue hypoperfusion and reduced oxygen supply as a result of several etiologies. An adequate supply of oxygen to the tissues is essential for the cells to maintain aerobic metabolism and vital functions. When perfusion pressure is insufficient to support minimal oxygen requirements or, in other words, when the average arterial blood pressure is low or the venous blood pressure is high, there is a change from aerobic to anaerobic metabolism with consequent organic dysfunction.

Etiology

The most frequent cause of HIS in the neonatal period is perinatal asphyxia, which may be caused by: 1. interruption of umbilical blood flow (ex.: compression of the umbilical cord); 2. insufficient transplacental gas exchange (ex.: placenta detachment); 3. inadequate placental perfusion in the mother (ex.: maternal hypotension); 4. a compromised fetus that does not tolerate stress of labor (ex.: intrauterine growth retardation); 5. failure to expand the lungs right after birth.

All pathological conditions that lead to prenatal, perinatal, or postnatal hypoxia and tissue hypoperfusion are etiologic factors of HIS. In any etiology, shock is an example of postnatal disease causing HIS.
Diagnosis of perinatal asphyxia

Several studies have shown that the Apgar score alone is not appropriate for the diagnosis of perinatal asphyxia. Preterm newborns have low Apgar scores without presenting fetal acidemia. There is a significant correlation between gestational age and Apgar scores in the first and fifth minutes of life. The more premature the newborn, the greater the probability of presenting low Apgar scores with cord blood pH within a normal range.\(^1\)

In term newborns, the Apgar score is not reliable for diagnosing perinatal asphyxia. Thorp et al. showed that 77.8% of depressed term newborns (1st minute and 5th minute Apgar score less than 7) presented cord blood pH greater than 7.10.\(^2\) Data obtained at our services show that 56.25% of term newborns with 1st and 5th minute Apgar scores less than 7 had cord blood pH greater than 7.10.\(^3\)

Moreover, the use of umbilical cord blood gas analysis as the criterion for diagnosis of perinatal asphyxia is also not reliable. King et al. compared two groups of term or near-term newborns (acidemic newborns with pH less than or equal to 7.0 and controls with pH greater than or equal to 7.20), with 5th minute Apgar scores greater than or equal to 7. There were no differences between the two groups as to the presence of clinical alterations in the neonatal period.\(^4\) Data from our services on the comparison of two groups of term newborns (one with umbilical cord blood pH less than 7.0, and the other with pH between greater than or equal to 7.0 and less than or equal to 7.20), showed that 16.7% and 53.8% of patients in the first and second groups, respectively, did not show any clinical alteration compatible with perinatal asphyxia in the neonatal period.\(^5\)

Based on these findings, the American Academy of Pediatrics reserves the term asphyxia for patients who meet the following criteria: 1. metabolic or severe, combined acidemia (pH less than 7.0) in arterial umbilical cord blood; 2. Apgar score of 0-3 for more than 5 minutes; 3. neonatal neurological manifestations (ex.: seizures, coma or hypotonia); 4. multisystemic dysfunction of organs (ex.: cardiovascular, gastrointestinal, hematological, pulmonary, or renal systems).

Pathophysiology

Pathophysiological alterations resulting from HIS can be observed at the systemic and cellular levels.

Systemic alterations result from a circulatory adaptation that occurs in HIS patients. The process of asphyxia causes a redistribution of cardiac output in order to preserve blood perfusion of the central nervous system, of the heart, and of adrenal glands. Peripheral tissues, abdominal viscera, and lungs are hyperperfused, in favor of the referred more noble organs. This is how the body tries to preserve the function of more noble organs. However, when the hypoxic-ischemic process becomes too intense and severe, the central nervous system, the heart, and the adrenal glands are also affected, with consequent clinical manifestations.\(^7\)

At the cell level, there is an insufficient supply of oxygen. Consequently, the cells have to continuously synthesize ATP in order to maintain their integrity and function. ATP synthesis depends on oxidation and reduction reactions that take place in the mitochondrion. Oxygen depletion causes a reduction in cell ATP synthesis. The available energy is no longer enough to maintain the cell membrane pump, which is essential for maintaining the normal ion gradient. After the oxygen supply to the mitochondrion is reestablished, there is excessive formation of oxidizing substances, which can also cause tissue injury. The increase in oxidizing substances causes peroxidation of polyunsaturated fatty acids in the cellular membrane, alterations in all intracellular amino acids, especially tyrosine, histidine, phenylalanine, methionine, and cysteine, in addition to oxidation of cellular nucleic acids.\(^8\)

The death of nerve cells can occur in two morphologically different ways: necrosis and apoptosis. The necrotic process is characterized by edema, cell membrane rupture, and intense inflammatory reaction, determined by intense and short insults. In the apoptotic process, in turn, the cell agonizes, death is slow and progressive and characterized by the reduction in size of nucleus and cytoplasm, chromatin condensation, and DNA fragmentation; this mechanism is activated by endonucleases. Weaker but prolonged insults cause apoptosis. Therefore, apoptosis can occur in the form of milder ischemic injuries, whereas necrosis can occur in those of more intense injuries.\(^9,10\)

Initially, in hypoxic-ischemic syndrome, there is a synaptic inactivation that occurs as an adaptive response. This inactivation is reversible and precedes a significant reduction in the supply of high-energy phosphates to the brain. When the injury renders irreversible due to the lack of energy to maintain ATPase-dependent pumps, neurotransmitters such as glutamate are released.\(^11\)

Excitatory amino acids have been involved as etiological agents of neuronal injury and hypoxic-ischemic syndrome. Glutamic acid, the most important excitatory amino acid found in the brain, is cytotoxic to neuronal cells. The neurons that release glutamate are activated during hypoxic events by the entry of calcium into the cell and by depolarization\(^12\) of these cells. Simultaneously, there is a reduction of glutamate-dependent ATPase in the presynaptic membrane, which contributes to maintaining high concentrations of extracellular glutamate, and also a prolonged stimulation of this receptor. The activity of excitatory amino acids such as glutamate and aspartate is mediated by several subtypes of receptors, especially N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). The NMDA receptor can be essential for the mechanisms of hypoxic-ischemic injury; it presents modulatory sites that regulate calcium inflow through ionic channels.\(^11,12\) Calcium will
cross ionic channels only if there is simultaneous activation of NMDA and glycine (a co-agonist) receptors and release of magnesium-dependent ionic channel blockade.13

The accumulation of cytosolic calcium is the major factor among the multiple injuries and series of irreversible events that trigger cellular death induced by hypoxic-ischemic syndrome and reperfusion. Calcium activates degradative enzymes such as endonucleases, proteases, and phospholipases.11,13

The increased concentration of calcium in the intracellular space may trigger several biochemical events and generate free radicals: 1. activation of phospholipase A2, causing increased formation of free radicals via cycloxygenase and lipoxygenase; 2. activation of nitric oxide synthase (NOS), allowing for the formation of peroxinitrite and free radicals; 3. activation of proteases, converting xanthine dehydrogenase into xanthine oxidase, and forming free radicals; 4. activation of phospholipase C, resulting in increased intracellular calcium stores.

The formation of free radicals can cause the release of additional amounts of neurotransmitter, excitatory amino acids, and may also influence the activation of the NMDA receptors.13

Clinical manifestations

According to the criteria established by the American Academy of Pediatrics, in order to establish the diagnosis of perinatal asphyxia there has to be neurological manifestations and multisystemic dysfunction.6 Since HIS causes significant reduction in oxygen supply to all body tissues, increased anaerobic metabolism, ischemia, acidosis, and hypercapnia with diffuse cellular lesion, clinical manifestations, involving several systems of the organism, should be expected.

Central nervous system

The extension and distribution of ischemic brain injury is determined by brain maturity and by severity and duration of the insult. In preterm newborns, due to cerebral immaturity, the clinical identification of asphyxia is more difficult than in term newborns. This indicates that findings that are normal and common for preterm newborns may indicate central nervous system depression in term newborns.

Hypoxic-ischemic encephalopathy (HIE) is the most widely studied and described clinical manifestation of perinatal asphyxia. Clinical findings are nonspecific; therefore, in order to differentiate HIE from other causes of brain injury, it is important to have access to perinatal history. Sarnat and Sarnat14 have established several criteria for the classification of HIE (Table 1). In HIE, patient clinical status deteriorates during the first three days of life, and death usually occurs between 24 and 72 hours of life.

Seizures may be the only neurological manifestation after an episode of asphyxia. Seizures normally occur during the first 24 hours of life, and are long-lasting and resistant to anticonvulsant treatment.

Cerebral edema can be an early manifestation of severe HIE, resulting in areas of irreversible cerebral necrosis, especially involving the temporal lobe; moreover, it can result in subsequent cerebral palsy. Clinically, the increase in intracranial pressure in newborns is manifest very late in the development of cerebral edemas. Clinical manifestations include a bulging and tense fontanel, central hyperthermia, seizures, and several neurological manifestations that are similar to those observed in hypoxic-ischemic encephalopathy. In these cases, extensive cerebral necrosis is already present.15

Cardiovascular system

The initial circulatory response after hypoxic-ischemic injury involves redistribution of cardiac output to body tissues, with increased strain of myocardial fiber (which is already under the effect of ischemia) possibly causing acute myocardial infarct and myocardial failure of various severities; moreover, there can be cardiomyopathy and necrosis of the papillary muscle of the tricuspid valve. The right ventricle in newborns is highly prone to ischemic injury since vascular lung pressure increases with hypoxia and acidosis. This hemodynamic event causes reduced circulation in the right ventricle with subsequent ischemia or necrosis. Laboratory tests show increased CK-MB; electrocardiogram exams present alterations compatible with ischemic injury or myocardial necrosis; and scintigraphic examinations of the myocardium show ischemic manifestations.16-18

Initially, there is sinus tachycardia followed by bradycardia and heart failure. The newborn presents hyperactivity of the precordium, increased or reduced pulse with peripheral perfusion deficit, and generalized edema. Heart murmur - due to necrosis of papillary muscle - and cardiac arrhythmia can also be present.

Respiratory system

Asphyxia is frequently associated with persistent pulmonary hypertension of the newborn (PPHN). Asphyxia may cause necrosis of the papillary muscles of the tricuspid valve, resulting in tricuspid valve regurgitation and increased pressure in the right atrium, in addition to causing right-to-left shunt during ventricular systole. Furthermore, the combination of redistribution of blood flow in the body after a hypoxic-ischemic event and of metabolic acidosis causes increased vascular pulmonary resistance and a subsequent increase in pulmonary artery pressure. The right-to-left shunt of blood not oxygenated by the oval foramen and by the patent ductus arteriosus is responsible for severe systemic hypoxemia. The result is a sum of all clinical effects of generalized tissue ischemia. This situation is extremely serious and requires intensive care and immediate treatment so that clinical status can be reversed.19
Table 1 - Stages of hypoxic-ischemic encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage 1 (mild)</th>
<th>Stage 2 (moderate)</th>
<th>Stage 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Hyperalert</td>
<td>Lethargic</td>
<td>Stuporose, comatose</td>
</tr>
<tr>
<td>Neuromuscular control</td>
<td>Over-sensitive</td>
<td>Impairment of</td>
<td>Impairment or absence of spontaneous movements</td>
</tr>
<tr>
<td></td>
<td>to stimulation</td>
<td>spontaneous</td>
<td>spontaneous movements</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Posture</td>
<td>Mild distal flexion</td>
<td>Strong distal flexion</td>
<td>Intermittent decerebration</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Overactive</td>
<td>Overactive</td>
<td>Underactive or absent</td>
</tr>
<tr>
<td>Myoclonia</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Seizures</td>
<td>Absent</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Complex reflexes</td>
<td>Normal</td>
<td>Suppressed</td>
<td>Absent</td>
</tr>
<tr>
<td>Suction</td>
<td>Active or a little weak</td>
<td>Weak or absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro reflex</td>
<td>Overactive</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Oculovestibular stimulation</td>
<td>Normal</td>
<td>Strong</td>
<td>Weak or absent</td>
</tr>
<tr>
<td>Tonic neck reflex</td>
<td>Slight</td>
<td>Strong</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic functions:</td>
<td>generalized,</td>
<td>generalized,</td>
<td>Both systems</td>
</tr>
<tr>
<td></td>
<td>sympathetic</td>
<td>parasympathetic</td>
<td>depressed</td>
</tr>
<tr>
<td>Pupils</td>
<td>Dilated, responsive</td>
<td>Miosis, responsive</td>
<td>Average, slightly</td>
</tr>
<tr>
<td>Breathing</td>
<td>Spontaneous, regular</td>
<td>Periodic</td>
<td>responsive, anisocoria</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Normal or tachycardia</td>
<td>Bradycardia</td>
<td>Variable, bradycardia</td>
</tr>
<tr>
<td>Airway secretions</td>
<td>Sparse</td>
<td>Profuse</td>
<td>Variable</td>
</tr>
<tr>
<td>Gastrointestinal motility</td>
<td>Normal or decreased</td>
<td>Increased</td>
<td>Variable</td>
</tr>
<tr>
<td>EEG</td>
<td>Normal</td>
<td>Low voltage, periodic pattern (awake)</td>
<td>Periodic or isoelectric</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>&lt; 24 hours</td>
<td>2 to14 days</td>
<td>Hours up to some weeks</td>
</tr>
<tr>
<td>Follow-up</td>
<td>100% normal</td>
<td>80% normal, abnormal if symptoms persist</td>
<td>50% of death, the another 50%, severe sequelae</td>
</tr>
</tbody>
</table>


Currently, bidirectional echocardiogram with color mapping allows visualization of tricuspid regurgitation and of the oval foramen jet. It also allows monitoring of pulmonary artery pressure and assessment of right ventricle function. If echocardiography is not available, and if shunt is predominantly via the ductus arteriosus, PPHN may be diagnosed through the measurement of PaO2 or preductal arterial oxygen saturation (right radial artery) and postductal saturation (descendent aorta or lower limbs), indicating oxygenation differences.

Meconium aspiration syndrome is frequently associated with HIS and PPHN.

**Metabolic disturbances**

Initially, there is hyperglycemia as a result of increased release of catecholamines and cortisol, followed by hypoglycemia caused by the excessive consumption of liver glycogen stores and, in some cases, caused by late hyperinsulinism.

Early hypocalcemia (total serum calcium less than 7mg/dl or ionic calcium less than 4mg/dl during the first 72 hours of life) is secondary to renal failure and transient reduction in parathyroid hormone secretion. Hydroelectrolytic disturbances are secondary to acute renal failure or syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Hyponatremia and natriuria occur during the rehabilitation phase of acute tubular necrosis, while hypercalcemia occurs during prolonged renal failure.

**Gastrointestinal tract**

Increased serum ammonia levels may be detected by liver failure.\(^\text{24,25}\) Hepatic lesions may develop into necrosis.

Insufficient visceral blood perfusion may cause ischemia in the intestinal loops, thus putting newborns, especially preterm newborns, at increased risk for necrotizing enterocolitis.

**Renal tract**

Oliguria (diuresis less than 1 ml/kg/hour) or anuria are very common in newborns who have been affected by HIS. SIADH, acute tubular necrosis (ATN) and dehydration are causes of oliguria and require differential diagnosis since they are frequent in asphyxiated newborns.

SIADH occurs due to hypophysial dysfunction secondary to ischemic aggression.\(^\text{23}\) Patients with SIADH reabsorb a great amount of free water at the level of the distal tubule, and develop oliguria, edema, and hyponatremia. ATN resulting from ischemic renal lesion is often combined with reduced urinary output and acute renal failure, which persists for several days or weeks.\(^\text{27,28}\) The differential diagnosis of these pathologies that cause oliguria is shown in Table 2.

Some newborns with HIS develop neurogenic bladder; the consequent urinary retention is not related to renal parenchymatous disease. It is important that the bladder be palpated during the differential diagnosis of oliguria and anuria in newborns with HIS in order to check for bladder distention secondary to neurogenic bladder.

**Hematological manifestations**

Disseminated intravascular coagulation (DIVC) in newborns is associated with situations of tissue hypoxia-ischemia; this condition is more frequent after cardiac arrest, perinatal asphyxia, and systemic hypotension (usually observed in septic shock).

The clinical manifestation of DIVC includes: bleeding in venipuncture sites, echymosis, hematomas, petechiae, hematuria, digestive hemorrhage, and melena. These symptoms are followed by clinical findings of hypovolemic shock, which vary according to the severity of the disease. Laboratory exams show lengthening of activated partial thromboplastin time test (APTT), prothrombin (PT) e thrombin (TT). Platelet count can be normal or reduced. When DIVC is associated with necrotizing enterocolitis or sepsis, thrombocytopenia becomes more important, and the coagulation factors (PT, APTT) may be normal or slightly altered.\(^\text{29}\)

**Treatment**

Newborns with HIS have a multisystemic clinical status with involvement of several systems and different levels of severity. In this sense, the therapeutic approach is complex, requiring attention to several different manifestations. In certain situations, opposing treatments may be recommended to handle different clinical manifestations. In these cases, it is necessary to assess the risks and benefits of each approach in order to make the most appropriate decision.

**General precautions**

HIS alters cardiac and respiratory functions. Therefore, it is necessary to continuously monitor respiratory frequency, heart rate, arterial oxygen saturation, and arterial pressure. Apnea is a frequently observed clinical manifestation in newborns with HIS due to CNS injury; in these cases, mechanical ventilation is recommended. Altered heart rates may result from CNS injury or from direct involvement of the cardiac muscle. Involvement of the cardiac muscle results in reduced heart contractility, causing low arterial blood pressure.\(^\text{30}\)

Newborns with HIS usually present oliguria. Monitoring of 24-hour urinary excretion and urine density are crucial for the diagnosis of injury and for the future planning of fluid therapy.

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**Table 2 - Differentiated diagnosis of oliguria**

<table>
<thead>
<tr>
<th></th>
<th>Urine density</th>
<th>Urea and Creatinine</th>
<th>Serum sodium</th>
<th>FENa</th>
<th>Weight</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
<td>&lt; 2.5</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>ATN</td>
<td>↓</td>
<td>↑</td>
<td>N / ↓</td>
<td>&gt; 2.5</td>
<td>↑</td>
<td>A</td>
</tr>
<tr>
<td>Dehydration</td>
<td>↑</td>
<td>N / ↑</td>
<td>N / ↑</td>
<td>&lt; 2.5</td>
<td>↓</td>
<td>N</td>
</tr>
</tbody>
</table>

N = normal  A = altered
FENa (fractional excretion of sodium) = [(Urinary Na/serum Na)/(Urinary urea/serum urea)]x100
Serum electrolyte concentration (sodium and potassium) within the first 24 hours of life is essential when establishing therapeutic approaches, and also important as a screening test for blood glucose, ionic calcium concentration (preferably) or total serum.

A chest x-ray upon hospital admission is important to rule out respiratory problems that may require immediate treatment (e.g., pneumothorax), and also helps to diagnose pulmonary diseases that might have triggered the hypoxic-ischemic process (e.g.: congenital pneumonia) or that could result from this process (e.g.: meconium aspiration syndrome). Arterial blood gas analysis is also important to investigate the partial pressure of blood gases and detect alterations in acid-base balance.

**Treatment of hypotension**

Hypotension in patients with HIS may result from loss of circulating volume (preload reduction), in the case of acute hemorrhages, or myocardial injury with involvement of heart contractility. The use of volume expanders (saline or total blood solution) is only recommended if the preload becomes reduced. In these cases, an infusion of 10 ml/kg of saline solution during 30 minutes is administered. This procedure can be repeated up to three times, if necessary, until blood pressure reaches normal levels.31

Vasoactive drugs are recommended to improve heart contractility. The most widely studied vasoactive drug in newborns is dopamine. Consequently, it is the most widely used. Dopamine at a dose greater than 5 micrograms/kg/min increases heart rate, contractility, and cardiac output.32 Though the action of dobutamine in newborns has not been widely studied, this drug has been used at a dose of 5 to 15 micrograms/kg/min, increasing contractility and cardiac output.

**Treatment of metabolic disorders**

Hypoglycemia is treated with IV infusion of 200 mg/kg of glucose (2 ml/kg of glucose solution) during 1 minute, followed by continuous infusion of glucose at 8 mg/kg/min.33

Asymptomatic hypocalcemia is treated with IV infusion of 6 ml/kg/day of calcium gluconate at 10%, with 9 mg of elementary calcium/ml. This infusion is reduced by half at every 24 hours until complete discontinuation. In cases of symptomatic hypocalcemia, 1 to 2 ml/kg of endovenous 10% calcium gluconate in 5 minutes are used, along with monitoring of heart rate, and followed by IV infusion of calcium gluconate at 10%, 6 ml/kg/day.34

Hypercalcemia, which may occur as a result of renal failure, is treated with ion-exchanging resins or salbutamol (infused or nebulized).35

**Venous hydration and fluid balance**

Newborns who have been affected by HIS should not be orally fed during the first 48 to 72 hours of life until their hemodynamic status is back to normal. The visceral ischemia that originates from the hypoxic-ischemic process poses several risks for newborn infants, involving gastrointestinal disorders that range from intolerance to oral nutrition to necrotizing enterocolitis and intestinal perforation.

Fluid retention is frequent in newborns with HIS, caused by SIADH, by transient increase in serum aldosterone, or by ATN.24,27,28,36 Initially, venous hydration is carried out with 60 ml/kg/day of glucose solution without the addition of electrolytes. Necessary changes in the infusion volume and in the amount of electrolytes are made according to weight gain, diuresis, urine density, and serum electrolyte concentration.

**Treatment of respiratory failure**

The monitoring of arterial oxygen saturation and arterial blood gas analysis helps to select the most adequate approach for respiratory support: oxygen tent, CPAP or mechanical ventilation.

In the presence of adequate ventilatory support, metabolic acidosis can be corrected by slow IV infusion of sodium bicarbonate.

**Treatment of seizures**

The etiological diagnosis of seizures should be considered. Although seizures in newborns with HIS usually result from involvement of the CNS as a consequence of hypoxic-ischemic syndrome, metabolic disorders should be taken into consideration.

Seizures secondary to HIS are treated with endovenous phenobarbital (treatment of choice), using a loading dose of 20 mg/kg. If no initial response is obtained, two additional doses of 10mg/kg, at intervals of 20 to 30 minutes should be administered until the seizure is controlled. Before administering additional loading doses of Phenobarbital, serum concentration should be checked. The maintenance dose is 4 mg/kg/day given twice daily.37

Phenytoin should be associated with anticonvulsant therapy when the response to Phenobarbital is not good. The loading dose should be 20 mg/kg, and the maintenance dose should be 5 mg/kg/day, given intravenously every 12 hours.38

**Hypothermia**

Selective brain hypothermia started during the first hours after hypoxic-ischemic injury with mild body hypothermia may be beneficial to newborns with HIS.

In 1988, Gunn et al. showed that newborns treated with selective brain hypothermia and kept with rectal temperature of 35.7 °C, and whose treatment was initiated 2 to 5 hours
after birth had a better evolution than the groups with selective rectal hypothermia at 37°C and 36.3°C, respectively. After observing a larger group of 40 newborns, the same group of investigators confirmed the observation that selective brain hypothermia associated with body hypothermia is beneficial to decrease the neurologic sequelae of babies born with HIS.40

Strategies for neuroprotection

Several therapeutic interventions have been used in laboratory experiments with the aim of protecting the CNS when submitted to hypoxic-ischemic injury (Table 3)11,41. The current clinical application of these interventions is currently limited, since they are useful to protect the CNS if used before asphyxia injury. If applied after the aggression, they are ineffective.

Table 3  Neuroprotection strategies in the hypoxic-ischemic syndrome

| 1. Preventing the accumulation of excitatory neurotransmitters in synaptic vesicles |
|---------------------------------|---------------------------------|---------------------------------|
| 1.1 prevention of late membrane depolarization |
| 1.2 inhibition of glutamate release |
| 1.3 administration of adenosine |
| 2. Preventing the accumulation of cytosolic calcium |
| 2.1 blockade of calcium channel agonists |
| 2.2 prevention of depolarization |
| 2.3 GABA agonists |
| 2.4 blockade of calcium channels |
| 3. Inhibiting the mechanisms triggered by cytoplasmic calcium overload |
| 3.1 inhibition of enzyme activation |
| 3.2 inhibition of NOS |
| 3.3 inhibition of free radical toxicity |
| 4. Preventing microvascular injury |
| 4.1 revascularization of vaso-occlusive lesions |
| 4.2 inhibition of reperfusion injury |

A recent study with 178 newborns with severe HIE revealed that age at start of spontaneous breathing, need for cardiac massage during neonatal resuscitation, and age at start of seizures were the neonatal findings most strongly associated with poor prognosis. The later the beginning of spontaneous breathing and the earlier the seizures, the stronger the probability of developing neurologic sequelae.43

Finally, it is important to stress that the incidence of cerebral palsy in newborns has not decreased. Clinical data show that in 20% of the cases, HIE results from a pre-delivery insult; in 35% of the cases, maternal problems are present, such as diabetes, delayed intrauterine growth, and infection, but there are no signs of fetal distress; in 10% of the cases, HIE results from postnatal problems; and in only 35% of the cases does it result from problems that are detected during labor44,45.

References


