Hypoxic-Ischemic Encephalopathy in the Term Infant

Ali Fatemi, MD, Mary Ann Wilson, PhD, Michael V. Johnston, MD*

KEYWORDS

• Hypoxia-ischemia • Neonatal encephalopathy • Apoptosis
• Oxidative stress • Hypothermia

Hypoxia-ischemia in the perinatal period is an important cause of cerebral palsy and associated disabilities in children. Cerebral palsy is one of the most costly neurologic disabilities because of its frequency (2/1000 births) and persistence over the life span.[1] In the term infant, the most common mechanism of hypoxic injury is intrauterine asphyxia brought on by circulatory problems, such as clotting of placental arteries, placental abruption, or inflammatory processes.[2] These factors result in perinatal depression, leading to diminished exchange of oxygen and carbon dioxide and severe lactic acidosis.[2] A recent study by Graham and colleagues[3] showed that the incidence of neonatal neurologic morbidity and mortality for term infants born with cord pH less than 7.0 is approximately 25%. Reduced cardiac output in the setting of hypoxia is referred to as hypoxia-ischemia (HI).[4] If an episode of HI is severe enough to damage the brain, it leads within 12 to 36 hours to a neonatal encephalopathy known as hypoxic-ischemic encephalopathy (HIE).[5] This clinical syndrome includes seizures, epileptic activity on electroencephalogram (EEG), hypotonia, poor feeding, and a depressed level of consciousness that typically lasts from 7 to 14 days.[6] Pathology studies of term neonates who sustained a profound hypoxic-ischemic event show relative cortical sparing and deep gray matter injury, particularly involving hippocampi, lateral geniculate nuclei, putamen, ventrolateral thalami, and dorsal mesencephalon.[7] There is no effective pharmacologic therapy, although hypothermia has shown promise in several clinical trials.[8,9] Magnetic resonance imaging (MRI) has markedly improved the understanding of the patterns of brain injury from perinatal asphyxia. The pattern produced by so-called near-total asphyxia is easily recognized on MRI scans and includes selective injury to the putamen, thalamus, and perirolandic cerebral cortex, and often involves the brainstem as well.[10] This pattern is similar to

Support received from NIH R01-NS028208-17A2.
Kennedy Krieger Institute, Department of Neurology, Johns Hopkins Medical Institutions, 707 N Broadway, Baltimore, MD 21205, USA
* Corresponding author.
E-mail address: Johnston@kennedykrieger.org (M. V. Johnston).

Clin Perinatol 36 (2009) 835–858
doi:10.1016/j.clp.2009.07.011 **perinatology.theclinics.com**
0095-5108/09/$ – see front matter

the pathologic pattern of diencephalic and brainstem injury described by Myers in a model of acute total asphyxia in nonhuman primates, developed in the early 1970s.[11] This injury can be distinguished from that produced by a partial prolonged insult that results in more extensive cortical injury. In most infants, white matter is relatively spared, although a transient increase in the T2-weighted MRI signal is often seen in the posterior internal capsule soon after injury.[12] Infants who demonstrate this pattern of insult may require vigorous resuscitation to survive, and have severe metabolic acidosis in the umbilical cord blood.[13] Metabolic derangements leading to oxidative stress, inflammatory factors, excitotoxicity, and perhaps genetic factors are thought to contribute to brain injury after HIE.

DELAYED CELL DEATH IN HIE

Clinical and experimental observations demonstrate that HIE is not a single ''event'' but is rather an evolving process. The clinical signs of HIE reflect the evolution of a delayed cascade of molecular events triggered by the initial insult. MRI studies show progression of lesion size over the first few days after injury (**Fig. 1**).[14] Initial findings within the first few hours after near-total asphyxia are subtle and often seen only on diffusion-weighted imaging, which shows restricted diffusion typically starting as small lesions in the putamen and thalami, and usually progressing over the next 3 to 4 days to involve more extensive areas of the brain.[14] MR spectroscopy shows a similar pattern of progression, with an increase in lactic acid and reduction of *N*-acetyl-aspartate over the first few days after initial insult (**Fig. 2**).[15] Studies of animal models of HIE show that during the period after the insult, many neurons and other cells ''commit'' to die or survive over a period of days to weeks.[16] Many of them might be rescued during this ''window of opportunity.'' Along with this notion, hypothermia has shown beneficial effect in HIE,[9] suggesting that intervention after birth is still helpful, possibly by preventing delayed cell death. Therefore, it is crucial to investigate molecular pathways involved in this event to identify potential therapeutic interventions.

Animal studies have led to new insights into HIE. Rodent models combine unilateral carotid artery ligation with exposure to a period of hypoxia to replicate the combination of hypoxemia and ischemia seen in human infants after asphyxia.[17] Comparison of histology from the animal model with MRI of human term infants after near-total asphyxia reveals remarkably similar patterns of injury to the basal ganglia and cerebral cortex.[10,13,16] Unilateral carotid ligation plus hypoxia results in predominant injury on one side with modest or no injury on the other.[18] These studies show that during the initial phase of HI there is rapid depletion of adenosine triphosphate (ATP),[19,20] leading to failure of Na/K-pump and depolarization of the cell, with severe cell swelling and cytoplasmic calcium accumulation, further leading to necrosis and activation of multiple cascades that eventually result in more cell death.

The form of cell death depends on the severity of ischemic injury.[21] Necrosis predominates in more severe cases, whereas apoptosis occurs in areas with milder ischemic injury, often days after the initial insult.[22] The authors have shown that activation of the proapoptotic protein, caspase-3, in a neonatal rodent model of cerebral hypoxia-ischemia is prolonged and that moderate to high levels of activated caspase-3 persist for at least 7 days after hypoxic-ischemic injury.[16] The regional and temporal patterns of caspase-3 activation correspond well with those for apoptosis,[16] lending further support for a prolonged role of apoptosis in hypoxic-ischemic injury in the neonatal brain. The newborn brain is primed to respond to various insults with activation of apoptotic cascades, due to the importance of programmed cell death in the