

Hypoxic Ischemic Brain Injury in the Developing Brain

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ABSTRACT

Hypoxic Ischemic Encephalopathy (HIE) is a common condition affecting babies and children. The specific prognosis depends on several factors, but normal brain development is often compromised. Treatment options are limited, so ongoing care is required to reduce pain and suffering and optimize health outcomes in this group of patients. Here, we review details of HIE and its impact on the developing brain, as well as therapeutic options and ways to ensure that patients receive the right type and level of care.

Keywords: Hypoxic ischemic encephalopathy; Brain; Prognosis; Infants

INTRODUCTION

Hypoxic Ischemic Encephalopathy (HIE), which arises when the brain is deprived of blood flow or oxygen, is a leading cause of death in infants and common in older children when cardiac arrest or drowning occurs [1-3]. Hypoxic ischemia is the most common cause of neonatal brain damage, occurring in 1.5 to 2.5 per 1000 live births in developed nations [1,4,5]. It is also one of the most serious birth complications affecting full-term infants. The risk of HIE is 60% higher in premature neonates compared to those who are not born prematurely [6].

Though the precise cause is not always known, when HIE occurs due to a birth complication, the cause often involves abruptio placentae, breech presentation, cord prolapse, maternal hypotension, placenta previa, shoulder dystonia, or uterine rupture [1]. By the age of 2, 40% to 60% of infants who have endured HIE have died or are experiencing severe disabilities.

Fortunately, obstetric care and neonatal care advancements have significantly reduced the morbidity and mortality associated with HIE. Nonetheless, they have not reduced the incidence of HIE, and patients who suffer HIE frequently endure lifelong disabilities and complications associated with their brain damage [1,4,6,7]. Understanding the nature of their challenges is critical

for ensuring that they get the right type and amount of care to protect their health and quality of life.

THE DEVELOPING BRAIN RESPONDS TO INSULTS DIFFERENTLY THAN THE ADULT BRAIN, MAKING CHILDREN VULNERABLE

The damage that results from HIE occurs in two phases: first, the damage that occurs in response to the initial injury as oxygen or blood flow are cut off from the brain, and second, when oxygen or blood flow are restored, and toxic mechanisms are activated. Because of the specific vulnerabilities of the young brain, HIE can disrupt development and lead to a variety of neurological disorders that include epilepsy, cerebral palsy, motor disturbances, and learning disabilities [4].

Normally, the immature brain is protected through adaptive mechanisms such as those that result in low energy demands. However, severe brain insults can cause a cascade of neurological events that may produce more severe outcomes in the developing brain compared to the adult brain [8-10]. The neuronal and white matter destruction that occur with HIE are due largely to

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the inflammatory cascade that is initiated upon injury, as well as apoptosis, oxidative stress, and excitotoxicity that ensue subsequently [3,4,11].

Inflammation

Inflammation is known to mediate injury induced by brain injury in people of all ages, and the mechanisms driving inflammatory responses are similar across age groups. However, the immature brain has been shown to display a unique inflammation phenotype that may help to explain its vulnerability to HIE [12].

Apoptosis

Apoptotic program initiation is thought to underlie most of the pathophysiology that occurs in neonatal brain disorders induced by hypoxic ischemia [13]. The propensity of neurons in the immature brain to die *via* apoptosis versus necrosis is likely a primary culprit for the vulnerability of the developing brain to HIE [14]. Though this activity pattern facilitates plasticity by enabling the pruning of redundant cells and structures, the apoptosis that occurs following HIE in the developing brain may contribute to long-term damage [15].

Oxidative stress

The developing brain is more vulnerable than the mature brain to free radicals because scavenging systems have not yet developed to attack those free radicals. Oxidative stress thus tends to occur at a higher rate in the context of cerebral ischemia in an immature brain than in an adult brain and likely promotes problematic apoptosis [16].

Excitotoxicity

Neurons with glutamate receptors, which transmit excitatory signals, have been shown to be especially sensitive to hypoxic-ischemic injury [17]. The developing brain experiences an upregulation of NMDA glutamate receptors, which likely makes brain cells in the immature brain particularly susceptible to excitotoxic injury [14].

In addition to these damaging mechanisms that distinguish immature brain and mature brain responses to hypoxic ischemia, the blood brain barrier may also play a role. Though the implications for HIE are unclear, the blood brain barrier appears to possess distinct physiological activity in newborns versus adults [18].

TREATMENT OPTIONS FOR HIE ARE LIMITED

Imaging can provide insights into the specific injuries in the developing brain, but even with knowledge of injuries, treatment options tend to be limited [19,20]. The physiological response to HIE can last for days or weeks and are thought to present a therapeutic window during which interventions may help to protect the developing brain [13]. Nonetheless, there are no interventions recommended based on randomized controlled

trials [7]. Research into the potential for several treatments, however, is ongoing.

Cooling

Hypothermia aims to protect the brain from the effects of reduced blood flow or oxygen by reducing body temperature and may minimize severe disabilities and death [21]. It is the only treatment that has been shown to be effective for HIE in neonates, though combination therapies that can help protect the injured brain and extend the therapeutic window are expected to emerge [22,23].

Anti-inflammatories

Given the inflammatory reaction to HIE that causes neuronal damage, the rationale for anti-inflammatories is clear [24]. However, the success of these drugs is currently limited to the promise of neuroprotection they have shown in preclinical studies [2].

Anti-excitotoxic and anti-apoptotic interventions

Because excitotoxicity and apoptosis appear to contribute to the damage induced by HIE, therapies that are anti-excitotoxic and anti-apoptotic have been proposed as strategies to salvage tissue in the brain following hypoxic-ischemia [8-10]. However, experts have pointed to the importance of determining whether the potential benefits of such therapies-particularly anti-apoptotic one-outweigh the potential harms [25].

Neurotrophins

Neurotrophins, including Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), and Neurotrophin-3 (NT-3) have also been suggested as offering therapeutic opportunities for HIE, as they play a clear role in regulating neuronal death during brain development [26]. However, their specific potential for protecting against injury induced by hypoxic-ischemia remains unclear.

Antioxidants

Though not approved by the U.S. Food and Drug Administration (FDA) or the European Medicine Agency for the treatment of HIE, antioxidants that are already established as neuroprotective appear to be good therapeutic candidates for HIE without adverse side effects [6].

Matrix Metalloproteinase (MMP) inhibitors

MMP inhibition has been shown in some research to provide acute and long-term benefits by reducing the degradation of tight junction proteins, supporting the integrity of the blood brain barrier, and improving edema in the brain following hypoxic ischemia in neonates [27].

Stem cell transplantation

Innovative new strategies like the use of stem cell transplantation to protect against further neurological damage

are also being explored for their relevance and application to HIE [28].

DISCUSSION

Ongoing care is essential for those who have suffered HIE

The prognosis for those with HIE depends on several factors, including how long the brain was deprived of oxygen or blood flow, what parts and to what extent the brain is damaged, and which functions are disrupted. Details of prognosis are difficult to determine, particularly for newborns [21]. However, there are some clues in certain contexts that can help to formulate prognoses. For instance, in cases where birth asphyxia has occurred, clinical neonatal seizures, independent of HIE severity, are associated with worse outcomes from a neurodevelopmental standpoint [29].

As more is learned about how the development of cerebrovasculature is affected by HIE, treatment options and types of care are likely to change [30]. For now, it is critical that the type and level of care provided to HIE patients match their needs to ensure the best possible outcome for this population of patients. While some aspects of care may only be relevant in the short-term following HIE, others may be important for the duration of the patient's life.

Supportive care should include seizure management-including prevention through careful blood glucose management as well as anticonvulsant administration-as well as maintenance of adequate ventilation, fluid management, balance of electrolytes, and avoidance of hypotension [31-34].

A multidisciplinary or interdisciplinary team that includes physiatrists, pediatric neurologists, pediatric orthopedic surgeons, pediatricians, and other relevant specialists are needed to optimize care [35]. In addition, ongoing monitoring and physiatric care, which depends on the individual's specific deficits, will likely be required. As the extent of disability is not always clear immediately following injury, patient needs may evolve over time, and the care provided should always reflect current needs [21].

CONCLUSION

While each case of HIE is unique, characteristics of the developing brain make younger patients more vulnerable to long-term neurological consequences. Though several of the mechanisms that drive the destruction that occurs with HIE are clear, there is no highly effective treatment option for those suffering from this type of brain injury. Given that the condition and its potential complications are well understood, ensuring that patients who have endured HIE are provided with the right level and amount of care can help ensure patients live longer, have a reduced amount of pain and suffering, and enjoy a higher quality of life.

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