The Clinical Problem: Neonatal hypoxic-ischemic brain damage

Hypoxia (a deficiency in oxygen availability), either alone, or in association with ischemia (a restriction in blood supply), can occur in individuals of all ages as a consequence of a stroke or cardiac arrest [1]. In the newborn, hypoxic-ischemic (HI) brain injury is a common occurrence during childbirth, arising as a consequence of complications such as placental abruption and umbilical cord compression [2]. Approximately 3% of all infants born worldwide experience HI events during birth and these events contribute significantly to infant death [3]. HI events are a common problem in the premature infant, affecting approximately 60% of babies born prior to 37 weeks’ gestation [4].

In Australia, at least four newborns per day will suffer a birth-related HI event. The incidence of mortality and long-term complications depends on the severity of the HI insult and occurrence of other complications such as seizures or cardiorespiratory failure. HI-related seizures typically occur within the first 24-48 hr after birth and are associated with increased brain damage [5, 6]. Up to half of newborns suffering severe HI injury do not survive the newborn period. Most deaths occur due to multiple organ failure or redirection of care. Another 25% of babies have permanent disabilities such as mental retardation, cerebral palsy, and epilepsy [7]. HI brain injury around the time of birth also has broader sequelae, causing emotional stress for the families of affected babies and creating a large economic burden on society for the long-term care of disabled individuals. There is an urgent need to develop novel therapies that protect the newborn brain since current treatments such as cooling (hypothermia) and management of seizures do not ensure normal developmental outcomes.

A healthy brain

A healthy brain requires the coordinated functioning of its cellular elements, namely neurons and glia. Neurons have long been the focus for neuroprotective strategies since they are the principal communicative cells of the brain while less attention has been given to the glial system of the central nervous system (CNS). Glial cells function to support neurons and include three subtypes – astrocytes, oligodendrocytes and microglia. Neurons cannot survive in the CNS without close interaction with glial cells. Astrocytes provide the link between blood vessels and neurons, and regulate molecules such as neurotransmitters, energy sources, water and ions. Astrocytes are thought to be more resistant to ischemia than other glial cells and respond to insults with early structure/function changes [8, 9] and later undergo ‘reactive gliosis’. Oligodendrocytes are the myelinating cells of the brain that, like neurons, are highly sensitive to injury by oxidative stress and glutamate toxicity. Microglia are the macrophage-like cells in the brain that are often activated in response to CNS injury or inflammation. Thus, all cells of the CNS play a role in HI brain injury and thus the key to providing protection for the newborn brain is to protect all the cells of the brain, including neurons and glia.

HI triggers a cascade of biochemical and molecular events that initially involve energy depletion, acid-base imbalance and alterations in neurotransmitter concentrations. After reperfusion, oxygen levels may be restored but the brain remains vulnerable to further injury.
that can be perpetuated by multiple biological pathways, commonly referred to as “secondary energy failure” [10]. Brain damage occurs because neuronal and glial cells die as a consequence of one or more cell death pathways (for example, oxidative stress, excitotoxicity, inflammation). This brain damage develops over a period of days to weeks; therefore, a therapeutic window exists for treatment or intervention [2].

**Current and future treatment options**

Current treatments for HI brain injury include management of seizures with anti-epileptic drugs and hypothermia. Seizures are often the first sign of neurological deficiency and are known to exacerbate HI-related brain injury. Unfortunately, anti-epileptic drugs (AEDs, such as phenobarbital) used to treat neonatal seizures are generally ineffective and have large potential for side effects in the developing brain. Current research is investigating alternative anticonvulsants (e.g., topiramate) or drugs that can be used in combination with AEDs (e.g., the diuretic bumetanide) to better control refractory seizures and improve outcomes.

Hypothermia (selective head or total body cooling) has recently become standard practice in neonatal intensive care units in tertiary hospitals. Cooling reduces metabolic demand and electrical activity, thereby reducing secondary energy depletion and cell death. Hypothermia is beneficial for infants with mild to moderate HI injury, with decreased mortality and long-term disability [11]. Hypothermic treatment is a major advance in the treatment of neonatal HI injury. However, more than 40% of hypothermia-treated infants still suffer poor neurological outcome, it is contraindicated in premature infants (<36 weeks’ gestation) and does not provide benefit if HI injury is severe. Furthermore, current clinical practice is that hypothermia will only be initiated within 6 hr of birth, which can be a major issue for Australian babies born outside of large tertiary hospitals (as found in major cities). A clinical trial in the USA is examining whether late hypothermia (within 6-24 hr of birth) improves outcomes in HI babies. Thus, there is an immediate and compelling need to investigate whether hypothermia can be combined with other adjunctive treatments to improve outcomes following HI brain injury. Current research is focussing on therapies that can either be used in conjunction with hypothermia (for review see [12]). Some promising therapies are currently in clinical trials in USA include xenon, melatonin, erythropoietin and umbilical cord-derived stem cell transfer (see [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). It is hoped that these therapies given before, during or after hypothermia will extend the therapeutic window or may provide additive neuroprotection. There are various pros and cons to consider for each therapy including ease of administration, cost and side effects. It is vital to examine the safety of combination therapies as risks include altered drug metabolism (by hypothermia) and adverse drug interactions. Furthermore, it is essential to ensure that these therapies do not disrupt or disturb the normal development of the newborn brain.

**Conclusion**

Neonatal HI brain injury remains a significant clinical problem and current treatments are inadequate. An ideal treatment strategy should protect all the cells of the brain, including neurons and glia and must not interfere with normal brain development. Developing therapies that prevent or reverse HI brain damage are essential for providing Australian babies a healthy start to life.
References: