Birth Asphyxia and Hypoxic-Ischemic Brain Injury in the Preterm Infant

Abbot R. Laptook, MD

KEYWORDS

• Hypoxia-ischemia • Asphyxia • Preterm infants • Therapeutic hypothermia
• Neuroprotection

KEY POINTS

- Identifying perinatal hypoxic-ischemic/asphyxial events in preterm infants is more challenging compared with infants ≥36 weeks' gestation.
- For the more mature preterm infant, extrapolation of criteria used in infants ≥36 weeks' gestation to identify perinatal hypoxia-ischemia may be feasible.
- For the extreme preterm infant, identification of perinatal hypoxia-ischemia that is linked to early childhood outcome is difficult given the many morbidities of prematurity; this will limit a targeted approach for neuroprotective treatments.
- A major knowledge gap is whether the neuropathology of hypoxic-ischemic injury among moderate and late preterm infants is similar to extreme preterm infants (arrest of pre-oligodendrocyte maturation) or term infants (selective neuronal necrosis) or a combination of the 2.

Identification of infants ≥36 weeks' gestation with perinatal hypoxia-ischemia or asphyxia has allowed investigation of potential neuroprotective treatments. Therapeutic hypothermia is the first therapy demonstrated to be efficacious for infants ≥36 weeks' gestation with hypoxia-ischemia or asphyxia. Multiple randomized trials demonstrated that relatively small reductions in core temperature alone or a combination of reduced head and core temperature (therapeutic hypothermia) reduces death or disability at 18 months.[1–5] Disability was typically severe and could be any of cognitive, motor, or sensory deficits. Neuroprotective effects of therapeutic hypothermia persist even at 6 to 7 years of age.[6,7] The importance of this therapy extends beyond the benefits provided to infants and their families; it signifies that hypoxic-ischemic brain injury is modifiable and has accelerated testing other potential neuroprotective

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Department of Pediatrics, Women and Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI 02905, USA
E-mail address: alaptook@wihri.org

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interventions either with or without therapeutic hypothermia.[8] Two National Institutes of Health Consensus conferences on therapeutic hypothermia have provided the neonatal community with guidance on dissemination and gaps in knowledge of this new therapy.[9,10]

It has been widely recommended that centers that offer therapeutic hypothermia follow studied protocols to ensure appropriate use in clinical practice. Analysis of therapeutic hypothermia implementation in the United Kingdom using the TOBY registry suggests consistency with prior clinical trials.[11] However, there is evidence of drift from evidence-based recommendations; in the TOBY registry, hypothermia treatment was provided to 2.8% of infants who were less than 36 weeks' gestation.[11] Similarly, 5.8% of infants in the Vermont Oxford Registry for encephalopathy between 2006 and 2011 were less than 36 weeks' gestation and received hypothermia treatment.[12] Outcomes of preterm infants undergoing hypothermia were not provided from either registry. In the absence of data from clinical trials, it is likely that therapies tested in more mature infants will be extended to preterm infants.

The objective of this report was to provide an overview of perinatal hypoxic-ischemic or asphyxial brain injury in preterm infants. Available information for preterm infants is contrasted with more mature infants (≥36 weeks' gestation). Hypoxic-ischemic brain injury is examined with advancing maturation from extreme to moderate to late preterm infants.

TERMINOLOGY

In clinical practice, the terms hypoxia-ischemia and asphyxia are often used interchangeably. Technically there are important differences. Hypoxia is a low content of oxygen in the blood, whereas ischemia represents a reduction in tissue blood flow. Ischemia in turn can be partial or complete in extent, and can be focal or global in distribution. Hypoxia and ischemia are often combined because each component may result in the other. In contrast, asphyxia indicates an impairment of gas exchange and is characterized by anoxia and extremes of hypercarbia. In the clinical setting, asphyxia is more commonly partial in severity, resulting in hypoxia and more moderate increases in CO_2 tension; ischemia may result if asphyxia is prolonged or severe. The potential modulating effect of hypercapnia is frequently overshadowed by hypoxia and ischemia.[13,14] Translating this potential broad range of physiologic perturbations into robust, easily applied, clinical criteria that distinguish asphyxia from hypoxia-ischemia is not possible with present tools. For these reasons, no attempt will be made to distinguish hypoxia-ischemia and asphyxia in this review of the preterm infant.

CRITERIA FOR THE DIAGNOSIS OF HYPOXIA-ISCHEMIA

For infants ≥36 weeks' gestation, a tiered set of criteria have emerged to diagnose hypoxia-ischemia shortly after birth. This includes identification of an event that can impair fetal gas exchange or objective evidence of altered fetal gas exchange. The newborn in turn needs to manifest biologic effects of impaired gas exchange. The latter is done by demonstrating the presence of encephalopathy because links between perinatal hypoxia-ischemia/asphyxia and childhood neurodevelopmental deficits almost always include the presence of neonatal encephalopathy. Different scoring systems for encephalopathy have been used with or without modification.[15,16] All trials of therapeutic hypothermia have used a tiered approach to establish a diagnosis of hypoxia-ischemia. As a first step, infants need to demonstrate clinical or biochemical indicators of impaired placental-fetal gas exchange. If the latter is present, infants then