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Challenges in neurologic prognostication after neonatal brain injury

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ABSTRACT

Parents often ask neonatologists and neurologists to determine neurologic prognosis in the preterm and term infant after neonatal brain injury. Prognostication in these populations remains rather full of uncertainties. Knowledge of available diagnostic tests and their limitations allows the clinician to synthesize the most likely outcomes after neurologic injury. In this review, we describe the diagnostic tools available to the clinician, active areas of research, and challenges in neurologic prognostication of the neonate.

Introduction

Prognostication after neurologic injury in neonates remains one of the most challenging aspects of neurological care in the neonatal intensive care unit (NICU). Neurologic prognostication in the NICU serves several purposes: first, to identify infants who may benefit from interventions; second, to counsel caretakers and parents regarding the need for developmental interventions after discharge; and third, to help inform discussions regarding continuation of life-sustaining interventions and end-of-life care.[1] Both preterm and term infants with either systemic injury or primary neurologic disease are at risk for abnormal neurodevelopmental outcomes ranging from mild neurologic impairments to profound intellectual disability, epilepsy or death. The main causes of morbidity and mortality in preterm infants with significant neurodevelopmental impairment are extreme prematurity, white matter injury, intraventricular hemorrhage and periventricular hemorrhagic infarction, while in term infants, neurological injury most commonly comes from hypoxic ischemic encephalopathy (HIE) or genetic disorders.[2,3]

Use of many of the life-sustaining interventions in the NICU hinge upon prognostication of the infant's possible neurodevelopmental outcome. As more interventions, such as therapeutic hypothermia directed at improving outcomes have arisen, the challenges regarding neurologic prognostication after brain injury have become more complex. Neurology consultants must reflect upon multiple aspects of the neonate in order to counsel caretakers and parents regarding the possible outcomes after neurologic insult.[4] In many instances, discussions about future neurological outcome will influence either end-of-life or limitation-of-treatment discussions in infants in the NICU. In fact, most neonatal deaths in the NICU follow withdrawal of life-supporting interventions in the face of prognostication of adverse neurodevelopmental outcome.[2,3]

In this review, we discuss general aspects of prognostication after severe neurological injury in neonates including the value of the neurological examination, ancillary clinical tests,

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and molecular biomarkers. We discuss active areas of research as well as specific challenges in prognosis in this special population.

General considerations in the neurological prognostication of infants

Preterm infants

Neonatologists and neurologists often face the need to prognosticate on neurodevelopmental outcome of preterm infants. These prognostic discussions are often challenging as many factors beyond neuroimaging can influence the outcome.

Clinicians frequently use cranial ultrasound imaging in the preterm infant, but while it may detect intraventricular hemorrhage and periventricular leukomalacia, ultrasound has limits for distinguishing non-cystic white matter or cerebellar injury. Because of this, the use of term-equivalent magnetic resonance imaging (TE-MRI) of the brain has gained popularity. Studies have shown that increasing white matter injury on TE-MRI correlates with increasing levels of cognitive impairment, although not all infants with severe white matter injury go on to develop disability.[5] TE-MRI can help stratify preterm infants to determine those who will require closer developmental follow up and early intervention, particularly those presenting with white matter injury.[5,6] However, the use of TE-MRI in preterm infants has also generated some controversy, with parents raising concern that acquisition of these images occurs without adequate counseling regarding the uncertainty of their prognostic value,[7] as well as the usefulness of the study while the infants remain in the NICU.[8] Nevertheless, in the appropriate setting, especially when considered in conjunction with neurologic and neurobehavioral assessments, TE-MRI can aid in prognostication of cerebral palsy and/or cognitive impairment as possible outcomes.[9,10]

Term infants

The most common disorders leading to end-of-life discussion in term infants are hypoxic ischemic encephalopathy (HIE), chromosomal abnormalities, and syndromic malformations. Despite the advent of therapeutic hypothermia, the single intervention shown to improve neurodevelopmental outcomes,[11] HIE continues to contribute to major world-wide neonatal mortality and to long-term morbidity in approximately half of the infants who survive the injury.[12] Clinicians use many diagnostic tests to prognosticate neurodevelopmental outcomes and death in infants with HIE and these are discussed in detail below. However, therapeutic hypothermia may alter the results of many of the neurophysiologic and other diagnostic tests when performed during the treatment, affecting their prognostic value.[13] These alterations should be taken into careful consideration when counseling caretakers and families regarding neurological prognosis. Even after therapeutic hypothermia, certainty in prognosis of infants with HIE remains a challenge, particularly in cases of moderate HIE.

Importantly, most of the literature on neurological prognostication of term infants has focused in patients with HIE. Studies investigating prognostic tools for other conditions are scarce and care must be taken to examine the data objectively, as inferences from the HIE population to other populations, such as neonates with infectious encephalitides, anatomical malformations, or metabolic disorders might not have validity.

Challenges in brain death determination in neonates

The determination of brain death in the pediatric population historically has stirred controversy, with concerns regarding variability. In 2011, the American Academy of Pediatrics, the Society of Critical Care Medicine, and the Child Neurology Society created a task force to update prior brain death determination guidelines and to standardize the determination of brain death in children, infants, and newborns.[14] The parameters included neonates over the gestational age of 37 weeks, and required two examinations by two different attending physicians. In addition to absent brainstem reflexes and flaccid tone with absence of spontaneous or induced movements, the neonate must undergo an apnea test. The guidelines do not require ancillary tests unless a portion of the physical examination or apnea test cannot be completed.

Determination of brain death in neonates is particularly difficult for several reasons. One cannot evaluate babies undergoing therapeutic hypothermia until after rewarming, since criteria for brain death determination requires normothermia. Neonates have greater sensitivity to some medications that can cause respiratory depression, possibly affecting the apnea test. In addition, the sleep state, presence or absence of sedation, or encephalopathy can alter the mental status of the neonate. The neonatal brain death guidelines attempt to address these factors, with recommendations regarding patient temperature, sedating medication use and elimination prior to assessment, and timing of examinations.[14] The clinician must know about these factors before undertaking a brain death evaluation. Also, the literature provides insufficient data for solid recommendations for determining brain death in infants less than 37 weeks of corrected gestational age.[14]

Diagnostic tests used in neurological prognostication

Clinical examination

In preterm infants, some neurologic examination findings, such as abnormal tone, have good sensitivity to detect infants at risk of poor neurodevelopmental outcomes.[15] Abnormal spontaneous and endogenous movements during the first 3 months of life have been associated with the development of cerebral palsy.[16] The finding of normal fidgety movements at 46–52 weeks postmenstrual age in preterm infants suggests with normal development and their