Advances in Neonatal Hypoxic-Ischemic Encephalopathy

Julia Konrad, MD[a], Vann Chau, MD[b], Thiviya Selvanathan, MD, PhD[c,*]

KEYWORDS

• Neonatal encephalopathy • Hypoxic-ischemic encephalopathy • Brain injury
• Term infant • Neurodevelopment • Neuroprognostication
• Magnetic resonance imaging • MR spectroscopy

KEY POINTS

- Despite advances in perinatal care and therapeutic hypothermia, neonatal hypoxic-ischemic encephalopathy remains a major cause of neonatal morbidity and mortality globally.
- Therapeutic hypothermia has significantly reduced mortality rates and severe disability and is standard-of-care for near-term/term infants with moderate-severe encephalopathy in high-income countries.
- Basal ganglia/thalamus pattern brain injury is associated with an increased risk for poorer motor outcomes, while watershed-pattern injury is associated with poorer cognitive outcomes.

INTRODUCTION

Neonatal encephalopathy (NE) is a clinical syndrome characterized by impaired neurologic function, including altered consciousness, seizures, abnormal tone and reflexes, feeding difficulties, as well as respiratory challenges. Hypoxic-ischemic encephalopathy (HIE) is the leading cause of NE in term or near-term neonates, affecting 0.5 to 3 per 1000 live births in high-income countries, with higher rates reported in low- and middle-income countries (LMICs).[1]

[a] Department of Pediatric Neurology and Developmental Medicine, Dr. von Hauner Children's Hospital, LMU Munich, Munich, Germany; [b] Division of Neurology, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada; [c] Division of Neurology, Department of Pediatrics, University of British Columbia, BC Children's Hospital Research Institute, Vancouver, BC, Canada
* Corresponding author. Department of Pediatrics, University of British Columbia and BC Children's Hospital Research Institute, 950 West 28th Avenue, Room V3-321, Vancouver, BC V5Z 4H4, Canada
E-mail address: Thiviya.selvanathan@cw.bc.ca

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Abbreviations

aEEG	amplitude-integrated electroencephalography
BGT	basal ganglia/thalamus
cEEG	continuous electroencephalography
cUS	cranial ultrasound
DWI	diffusion-weighted imaging
HIE	hypoxic-ischemic encephalopathy
LMIC	low- and middle-income country
MR	magnetic resonance
MRS	magnetic resonance spectroscopy
NAA	N-acetylaspartate
NE	neonatal encephalopathy
PAIS	perinatal arterial ischemic stroke
PLIC	posterior limb of internal capsule
WMI	white matter injury
WS	watershed

Despite advances in perinatal care, HIE remains a major cause of neonatal morbidity and mortality globally.[2] Survivors of HIE are at high risk for lifelong neurodevelopmental impairments, which imposes substantial social and economic burdens on families and health care systems. This article provides a clinically focused overview of HIE in term neonates, highlighting key investigations, management strategies, neurodevelopmental outcomes, and areas in need of further study.

PATHOPHYSIOLOGY OF NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Phases of Injury in Neonatal Hypoxic-Ischemic Encephalopathy

Neonatal HIE arises from disrupted oxygen delivery or blood flow during the peripartum period, leading to brain injury through early *necrosis, oxidative stress, programmed-cell death,* and *inflammation.*[3]

In HIE, brain injury evolves through distinct phases, each characterized by specific pathophysiological mechanisms, as outlined in **Fig. 1**.[3–7]

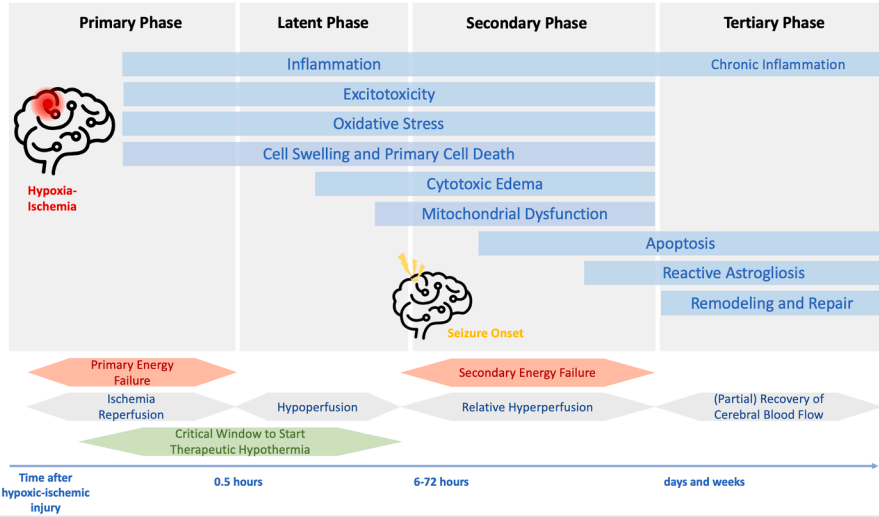


Fig. 1. Phases of hypoxic-ischemic brain injury progression in neonatal hypoxic-ischemic encephalopathy.

- *Primary phase* occurs immediately after the insult and arises from the abrupt reduction of oxygen and glucose supply, leading to primary energy failure. This phase is marked by acute cell swelling, lysis, and extracellular accumulation of excitatory neurotransmitters including glutamate, which triggers excitotoxicity and oxidative stress.
- *Latent phase* follows lasting approximately 6 h during which oxidative metabolism temporarily recovers although critical injury mechanisms, such as excitotoxicity, oxidative stress, and neuroinflammation continue to evolve.
- *Secondary phase*, typically lasting 48 to 72 h, represents a period of secondary energy failure driven by mitochondrial dysfunction, cytotoxic edema, neuroinflammation, and extensive programmed cell death through apoptosis and autophagy.
- *Tertiary phase* extends over weeks, months, or even years, involving chronic processes, such as persistent inflammation, impaired oligodendrocyte maturation, disrupted proliferation and synaptogenesis, and prolonged astrocyte activation. However, this stage is an important target for therapies focused on enhancing brain recovery and repair after injury.

Therapeutic hypothermia is most effective when initiated during the latent phase.[4,6] The neuroprotective effects of therapeutic hypothermia include reducing energy consumption, limiting the accumulation of extracellular glutamate, decreasing the generation of reactive oxygen and nitrogen species, inhibiting inflammatory pathways, and interrupting molecular cascades that lead to apoptosis.

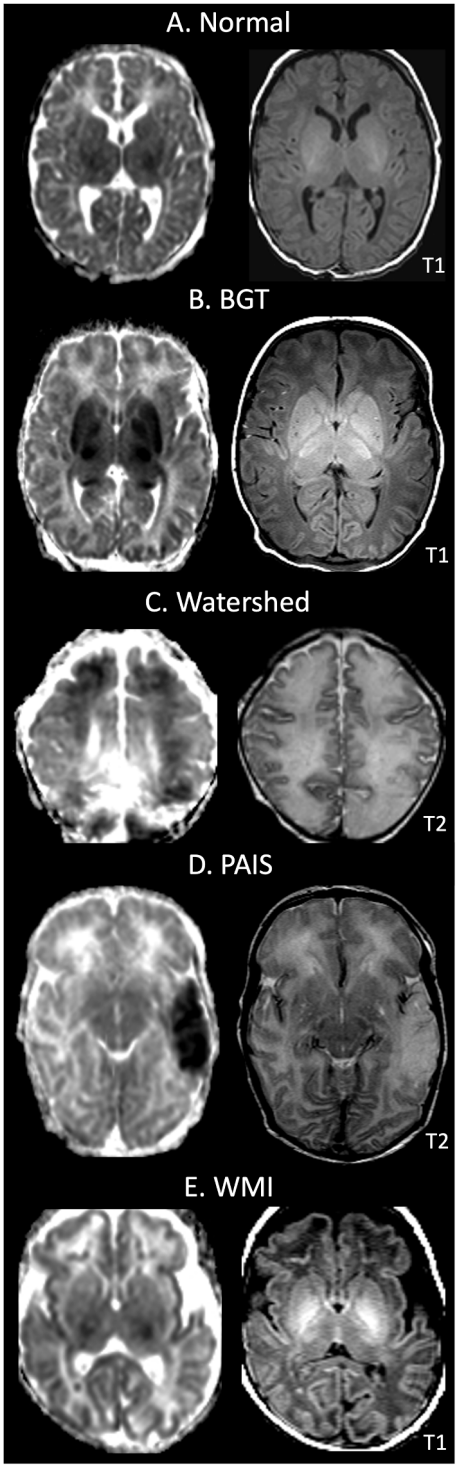
Key Patterns of Hypoxic-Ischemic Injury and Contributing Mechanisms

Fig. 2 illustrates the most common patterns of hypoxic-ischemic injury seen in neonatal HIE. The 2 primary patterns—basal ganglia-thalamus (BGT) pattern and watershed (WS) predominant—are distinct in their radiologic appearance. However, neonates with HIE frequently have mixed injury patterns reflecting the complexity of perinatal hypoxic-ischemic insults and contributing to significant variability in neurodevelopmental outcomes.[8]

The *BGT-predominant pattern* is most seen with acute and profound hypoxic-ischemic insults or sentinel events, such as uterine rupture, placental abruption, cord prolapse, or severe fetal heart rate abnormalities. This pattern predominantly affects the basal ganglia and thalami, with additional involvement of the perirolandic cortex, hippocampi, and corticospinal tracts.[9–11] This pattern of injury is observed in approximately 25% to 75% of infants with HIE.[8]

The *WS-predominant pattern* of brain injury arises from partial-prolonged hypoxic-ischemic insults involving the cortex and subcortical white matter located in the intravascular border-zones of blood supply between the anterior, middle, and posterior cerebral arteries.[9,11] This pattern occurs in approximately 15% to 45% of neonates with HIE.[8]

Less frequently observed patterns of hypoxic-ischemic brain injury in neonatal HIE include white matter injury (WMI) and perinatal arterial ischemic stroke (PAIS). WMI is predominantly seen in premature infants (Article-Advances in Preterm Brain Injury) and term infants with congenital heart disease (Article-Cardiovascular hemodynamics and brain health in congenital heart disease). Infants with HIE with WMI may present with milder degree of encephalopathy.[12,13] PAIS is an important differential diagnosis of NE and occurs in approximately 4% of neonates undergoing TH for HIE (reviewed in article- Perinatal stroke: From epidemiology to optimized outcomes).[8,14]



CLINICAL PRESENTATION

Neonatal Encephalopathy

Accurate assessment of severity of NE is critical in infants with HIE as it informs clinical management, including whether the infant is eligible for therapeutic hypothermia. Clinical and neurologic scoring systems remain central to this evaluation process; the *Modified Sarnat Score* and *Thompson Score* are 2 widely used scoring systems.[15,16] The neurologic presentation of HIE also evolves over time as outlined in **Fig. 3** and reflects evolution of underlying pathophysiologic processes contributing to brain injury.[15,17] Seizures are common in neonatal HIE and occur in approximately half of neonates with moderate-to-severe HIE (reviewed in article- Seizures in the neonatal period: a practical review from etiology to outcome).[18,19]

Non-neurologic Organ Dysfunction

While neurologic dysfunction is the hallmark clinical manifestation of HIE, non-neurological organ dysfunction is a frequent and significant contributor to morbidity and mortality in affected neonates.[20] The primary mechanism underlying multi-organ dysfunction in HIE is global hypoxia resulting from interrupted placental blood flow.[21] This triggers a compensatory redistribution of blood flow, shunting blood away from splanchnic, skin, and peripheral tissues toward vital organs such as the brain, heart, and adrenal glands to protect these organs from hypoxic-ischemic injury.[22] Despite this adaptive mechanism, organs outside the prioritized circulation, particularly the lungs, liver, kidneys, and heart, remain highly vulnerable to ischemia.[20,23] Pulmonary and hepatic dysfunction is estimated to occur in approximately 85% of neonates with HIE, renal dysfunction in 70%, and cardiac dysfunction in 60% to 75%.[21,24]

DIAGNOSTIC APPROACHES

Brain MRI

Brain MRI is the gold standard neuroimaging tool for evaluating injury pattern and severity in neonatal HIE.[8] The interpretation of findings is closely tied to the timing of imaging, given the evolving injury patterns over the first 2 weeks of life. Current literature recommends to perform MRI immediately after TH (i.e. 4 – 5 days of life) to assess the full extent of brain injury and optimize outcome prediction before pseudo-normalization of diffusion-weighted imaging (DWI) changes that occurs later in the first week of life.[25] Repeat MRI should be considered between 10 and 14 days of life if there is a significant discrepancy between clinical presentation and early imaging findings. Early MRI (within the first 2 days of life) may be appropriate in critically-ill neonates in some situations, such as when considering redirection of care. **Table 1** provides a comprehensive overview of recommended brain MRI sequences.

Cranial Ultrasound

Cranial ultrasound (cUS) is the most used neuroimaging technique in neonatal intensive care units due to its accessibility, non-invasiveness, and ability for bedside

Fig. 2. Patterns of hypoxic-ischemic brain injury in neonatal hypoxic-ischemic encephalopathy visualized on neonatal brain MRI (*left* = apparent diffusion coefficient image; *right* = T1-or T2-weighted image) performed 3 to 5 days of life showing (*A*) no injury, (*B*) basal ganglia-thalamus (BGT) pattern injury, (*C*) watershed pattern injury, (*D*) perinatal arterial ischemic stroke (PAIS), and (*E*) white matter injury (WMI).

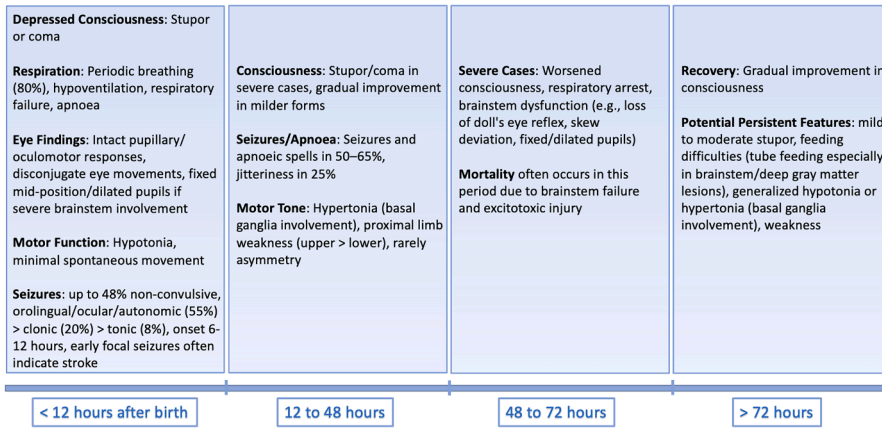


Fig. 3. Temporal evolution of encephalopathy in neonatal hypoxic-ischemic encephalopathy.

application immediately after birth and during follow-up evaluations over months. It is particularly effective in identifying gross brain malformations, intracranial and parenchymal hemorrhages, and findings suggestive of antenatal brain injuries, such as ventricular dilation and cystic lesions in the periventricular white matter.[9] However, cUS has limitations in detecting smaller or more subtle lesions, especially in the frontobasal, parasagittal, cortical, or brainstem regions, as well as identifying white matter alterations seen in neonatal HIE.[26,27]

MANAGEMENT

Therapeutic Hypothermia

Therapeutic hypothermia is considered as the standard-of-care for neonates with moderate to severe HIE in high-income countries, demonstrating significant reduction of mortality and neurologic morbidity across studies.[28] The neuroprotective effects of therapeutic hypothermia depend on 3 key factors: timing, depth, and duration. Early initiation is critical, ideally before the onset of delayed energy failure and excitotoxicity, which typically occurs around 6 hours after birth. Effective therapeutic hypothermia involves lowering the body temperature by 3 to 4°C to maintain a target temperature of 33 to 34°C for 72 hours.[6]

Neonatal Neurocritical Care and Supportive Management

Supportive care for neonates with HIE requires a multidisciplinary team, including neonatologists, neurologists, nurses, radiologists, rehabilitation specialists, and parents and families. Comprehensive neuromonitoring includes cardiorespiratory and temperature monitoring, along with continuous electroencephalography (cEEG), amplitude-integrated electroencephalography (aEEG), and near-infrared spectroscopy. Early nutritional support through enteral or parenteral feeding is essential to promote cerebral metabolism and overall growth. Developmental care interventions, such as optimal positioning, facilitated tucking and skin-to-skin care, have been shown to reduce stress.[29] Reducing painful exposures also support infant well-being and development.[30] Additionally, parental involvement and education play a crucial role in long-term outcomes, as counseling and communication empower parents to engage actively in care, facilitate bonding, and ensure consistent follow-up engagement beyond discharge from the neonatal intensive care unit.[31]

Table 1
Summary of MRI sequences, their clinical applications and key findings in neonates with hypoxic-ischemic encephalopathy

MRI Sequence	Clinical Application	Key Findings
Diffusion-Weighted Imaging (DWI)	• Highly sensitive for acute ischemic injury. • Detects abnormalities beginning at 24 – 48 hours of life; peaks at 3 – 5 days of life. • Pseudo-normalization occurs by 6 – 8 days of life.	• Increased signal intensity in areas with acute ischemic injury. • Important for detecting pattern and severity of hypoxic-ischemic brain injury in acute period.
Apparent Diffusion Coefficient (ADC)	• Complements DWI in assessing acute injury.	• Low ADC values indicate early ischemic injury.
T1-Weighted Imaging	• Evaluates myelination, ischemia, and subacute hemorrhage. • Assesses subacute and chronic injuries (e.g., gliosis). • Subtle alterations in the first days of life, changes become more evident day 10 – 14 of life.	• Hyperintensities in injured areas in subacute phase. • Decreased signal of posterior limb of internal capsule (PLIC). • Chronic findings: gliosis, encephalomalacia, brain atrophy.
T2-Weighted Imaging	• Assesses subacute and chronic injury. • Subtle alterations in the first days of life, changes become more evident day 10 – 14 of life.	• Hyperintensities in injured areas in subacute phase. • Chronic findings: gliosis, encephalomalacia, brain atrophy.
Magnetic Resonance Spectroscopy (MRS)	• Detects metabolic alterations in lactate. • Early and sensitive marker of injury.	• Elevated lactate most pronounced in basal ganglia and thalamus.
Susceptibility-Weighted Imaging (SWI)	• Identifies microhemorrhages or mineralization.	• Small hemorrhagic lesions or calcifications from hypoxic injury may persist for months.
MR Venography (MRV) ± Angiography (MRA)	• Consider when suspecting cerebral sinovenous thrombosis or perinatal arterial ischemic stroke as alternative etiologies of neonatal encephalopathy.	• Visualize filling defects that are suspicious for thrombosis.

NEURODEVELOPMENTAL OUTCOMES

Neonates with HIE face an increased risk for neurodevelopmental impairments affecting multiple domains of development, including motor function, cognition, and neurosensory abilities.[32]

Motor Function

Among term survivors of hypoxic-ischemic brain injury, more than one-third develop cerebral palsy or severe disability, with the highest incidence in those with severe encephalopathy.[33,34] Spastic quadriparesis is the most prevalent form of cerebral palsy, though athetoid and spastic hemiparesis also occur. Additionally, minor motor impairments that do not meet the diagnostic criteria for cerebral palsy are diagnosed in over one-third of children with moderate encephalopathy and over one-quarter of those with mild encephalopathy.[35,36] Comprehensive assessments of neurosensory and cognitive function are crucial for children with cerebral palsy.

Cognition

Cognitive deficits are reported in 30% to 50% of childhood survivors of moderate HIE.[37] Intellectual performance is often affected in children with severe encephalopathy, even in the absence of cerebral palsy.[38] School-age survivors of moderate NE frequently struggle with reading, spelling, and arithmetics, often requiring additional educational support.[39] Even when intelligence quotient (IQ) scores fall within the normal range, deficits in language and memory can be present. Additionally, behavioral challenges, such as hyperactivity and emotional difficulties, should be considered, even in children without motor impairments.[38]

Vision and Hearing

Severe visual impairment or blindness occurs in up to one-quarter of children with moderate to severe encephalopathy, particularly in cases of hypoglycemia. Visual dysfunction is commonly attributed to injury to the posterior visual pathway, including the primary visual cortex, leading to cortical visual impairment.[40] Brain injuries affecting the basal ganglia and thalamus are linked to deficits in visual acuity, visual fields, and stereopsis.[41] Sensorineural hearing loss, likely due to brainstem injury, affects up to 18% of survivors of moderate encephalopathy without cerebral palsy.[42]

Therapeutic Hypothermia and Neurodevelopmental Outcomes

While therapeutic hypothermia has reduced mortality rates and severe disability (number needed to treat 7; 95% CI 5 – 10),[28] a meta-analysis of 3 randomized controlled trials found that among cooled infants with HIE—26% died, 28% developed major neurodevelopmental disabilities, 26% had cerebral palsy, 8% were blind, and 5% were deaf.[43] Behavioral disorders are also prevalent in children with neonatal HIE.[44] Furthermore, a study assessing long-term cognitive outcomes found that 47% of cooled children had an IQ below 70 at 6 to 7 years of age.[45] Even children with higher IQs may experience difficulties with learning, attention, executive function, and memory, which may not become apparent until school age.[46–48] A recent multicenter cohort study reported that children with mild HIE had significantly lower cognitive scores than healthy controls at 2 y of age.[49] It is also important to note that TH may not have the same benefit in LMICs.[50,51] Even with therapeutic hypothermia, epilepsy remains a common sequela, with up to 18% of infants treated with therapeutic hypothermia experiencing seizures or infantile spasms at follow-up.[52]

To ensure optimal development, infants with HIE should be followed longitudinally in multidisciplinary neonatal neurodevelopmental programs, involving developmental pediatricians, neurologists, and therapists. These programs facilitate close monitoring and early intervention. Follow-up should continue at least until 3 y of age, with school-age follow-up preferred.

Predictors of Outcomes

Key predictors of neurodevelopmental outcomes in neonatal HIE are summarized in **Table 2**.

Magnetic resonance biomarkers

Patterns of brain injury and scoring systems. Since the initial classification of injury patterns, various scoring systems have been developed. Before therapeutic hypothermia became widespread, the *Barkovich scoring system* described 2 predominant patterns of injury linked to different hypoxic-ischemic events: BGT and WS patterns.[53] Originally based on T1-and T2-weighted imaging, this system later incorporated DWI and was found to correlate with outcomes.[11,54] In contrast, the *Rutherford scoring system* did not include DWI and was applied to imaging obtained after the first week of life, limiting its clinical usefulness when early decisions are needed.[55] Notably, abnormal signal intensity in the posterior limb of internal capsule (PLIC) strongly predicts motor outcomes and is a highly reliable marker of neurodevelopment prognosis.[56] The *Neonatal Research Network scoring system* categorizes injury severity on a scale from 0 (normal) to 3 (extensive cerebral hemispheric devastation) but does not incorporate DWI.[57] Similar to the Barkovich and Rutherford systems, this model has been validated as a predictor of mortality and disability at 18 months and remains predictive of early childhood outcomes.[58]

Table 2
Predictors of neurodevelopment outcomes in neonatal hypoxic-ischemic encephalopathy

	Predictive of Poorer Outcome
Neuroimaging Findings	
Pattern of brain injury	• Basal ganglia/thalamus ± PLIC injury associated with poorer motor outcomes. • Watershed injury associated with poorer cognitive outcomes.
Brain injury scoring systems	• Greater brain injury severity associated with poorer outcomes.
MR Spectroscopy	• Elevated lactate and reduced NAA associated with poorer outcomes.
Clinical Factors	
Encephalopathy	• Persistent encephalopathy associated with poorer outcomes.
Seizures	• Greater seizure burden, seizures during rewarming and refractory seizures associated with poorer outcomes.
Neurophysiologic Measures	
aEEG/cEEG background	• Low voltage, burst suppression, or flat trace associated with poorer outcomes. • Sleep-wake cycling within 36 hours of life predicts favourable outcome.

Abbreviations: aEEG, amplitude-integrated electroencephalography; cEEG, continuous electroencephalography; MR, magnetic resonance; NAA, N-acetylaspartate; PLIC, posterior limb of the internal capsule.

More recent scoring systems are more comprehensive. For example, the *Weeke scoring system* integrates proton magnetic resonance spectroscopy (H1-MRS) along with standard magnetic resonance (MR) sequences.[59] It evaluates gray matter (BGT, PLIC, perirolandic cortex, brainstem, and hippocampus), white matter/cortex (cortex, periventricular white matter, optic radiations, and corpus callosum), and the cerebellum, incorporating additional pathologic findings.[59] Of the various components, the gray matter subscore has been the strongest predictor of neurodevelopment outcomes at 18 to 24 months and school age.

Taken together, the scoring systems described earlier point towards two main findings:

- Gray matter injury ± abnormal PLIC consistently predict poor motor outcome.[11,56,60]
- Extensive WS injury correlates with poor cognitive outcome.[11,60]

Beyond established scoring systems, other brain regions also contribute to outcome prediction. Notable areas of interest include punctate white matter lesions, as well as injuries affecting the brainstem, cerebellum, mammillary bodies, hippocampus, and cases of global hemispheric injury.[57,61,62]

Magnetic resonance spectroscopy. MRS is a valuable tool for measuring changes in specific brain metabolites within a given region of the brain, and N-acetylaspartate (NAA) and lactate are particularly useful for evaluating brain injury. NAA is an acetylated-amino acid found in high concentrations within neurons of the central nervous system, with levels increasing as cerebral maturity advances.[63] A decrease in NAA levels is associated with cerebral injury or impaired cerebral metabolism.[64] Lactate is normally produced in the brain by astrocytes and used as fuel by neurons to replenish energy stores via oxidative phosphorylation.[64] Elevated lactate levels indicate disruptions in brain energy substrate delivery and oxidative metabolism, as seen in hypoxia-ischemia. The combination of increased lactate and reduced NAA levels is highly predictive of neurodevelopmental outcomes following neonatal brain injury.[65]

Other biomarkers

Beyond MR biomarkers, several clinical, biochemical, and neurophysiologic factors have been associated with outcomes in HIE. These predictors help guide prognostication, goals of care, and family counseling.

Clinical factors. Key clinical indicators of outcome include low Apgar scores, severity of encephalopathy, heart rate variability, and the presence of seizures. A low 10-min Apgar score has been consistently linked to increased risk of death and adverse neurodevelopment outcomes. Each 1-point decrease is associated with a 45% increase in the odds of death or disability.[66] The initial Sarnat stage of HIE, assessed within the first 6 hours of life, correlates with neurodevelopment outcomes.[67] However, some studies suggest that changes in encephalopathy severity over the first 4 days of life are better predictors of outcome than the initial classification.[68] The Thompson score has also been shown to predict outcomes, with scores $\leq$10 associated with normal cognitive function[69] and scores >12 linked to adverse outcomes.[70] Decreased heart rate variability at 24 to 48 hours, indicative of autonomic dysfunction, has been associated with adverse outcomes at 2 years.[71] High seizure burden, multifocal seizures, and treatment-refractory seizures have also been linked to poor outcomes.[72–75] Notably, the emergence of seizures during therapeutic hypothermia or rewarming has been associated with increased mortality and disability at 2 years[76] and a higher risk of epilepsy at 12 months.[77]

Biochemical factors. Several biochemical markers are associated with neurodevelopment outcomes. For example, a low initial arterial pH[78] and elevated lactate levels[79] have been linked to increased mortality, more severe brain injury on MRI, and cerebral palsy. Additionally, hypoglycemia, hyperglycemia, and glucose variability in infants with HIE have been associated with adverse neurodevelopment outcomes.[80,81]

Neurophysiologic tests. Neurophysiologic tests provide important insights into prognosis. Early studies showed that absent visual, brainstem auditory, and somatosensory evoked potentials were associated with poor outcomes.[82] However, therapeutic hypothermia appears to modify these associations. More recent research found that absent or prolonged latencies in somatosensory evoked potentials were not good predictors of neurodevelopment outcomes.[83] aEEG findings also provide prognostic value. Low voltage or burst suppression patterns have been linked to death or severe disability,[84,85] while the reappearance of sleep-wake cycling within 36 hours is indicative of more favorable outcomes.[86] Similarly, low voltage, burst suppression, or a flat trace on cEEG is associated with poor outcomes,[87] particularly if these patterns persist at 48 hours.[88]

Interestingly, a recent retrospective study of 182 neonates with HIE managed with therapeutic hypothermia found that the combination of EEG background during the first few days of life and the predominant pattern of injury on MRI provided the most reliable prediction of death and long-term disability. Evoked potentials added little prognostic value to this model.[89]

FUTURE DIRECTIONS

It is important to note that despite advances in perinatal and neonatal care, infants with HIE continue to experience a high burden of disability. Thus, there is a need for complementary neuroprotective and neurorestorative therapies (e.g. stem cells, melatonin) to improve neurodevelopment outcomes in neonatal HIE.[4,6] This is especially important given recent evidence suggesting that the neuroprotective effects of therapeutic hypothermia may be more limited in LMICs.[50,51]

A recent multi-center study of neonatal HIE demonstrated considerable variability in outcomes amongst infants who did not have severe brain injury on neonatal MRI, highlighting a need for novel neuroimaging biomarkers that are predictive of neurodevelopmental outcomes. Quantitative neuroimaging methods that assess measures of brain maturation have demonstrated smaller regional brain volumes and impaired myelination in neonates with HIE compared to healthy controls.[90,91] Smaller regional brain volumes and alterations in brain connectivity seem to persist to at least school-age in children with HIE and may be related to school-age neurodevelopment outcome.[92–96] These markers warrant further study to improve our counseling for families about expected neurodevelopmental outcomes and more accurately identify infants at high-risk for neurodevelopment impairments. Further studies of long-term neurologic and neurodevelopment outcomes after neonatal HIE in the post-cooling era are also needed.

CLINICS CARE POINTS

- Therapeutic hypothermia, detection and treatment of acute symptomatic seizures, treating non-neurologic organ dysfunction and neurodevelopmental care are all important aspects of NICU care to promote neurodevelopment in neonates with HIE.
- The optimal timing for brain MRI to assess brain injury pattern and severity in neonatal HIE is between 4-5 days of life after completion of therapeutic hypothermia to assess for acute

changes, or between 10-14 days of life to assess for subacute changes. A brain MRI performed in between these two periods may underestimate the full extent of injury due to pseudonormalization.

- Hypoxic-ischemic brain injury pattern and severity are important predictors of neurodevelopmental outcomes in neonatal HIE.
- Despite therapeutic hypothermia, neonates with HIE remain at high-risk for neurodevelopmental concerns and should receive neurodevelopmental screening and monitoring after discharge from the Neonatal Intensive Care Unit.

DISCLOSURES

None.

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