Hypoxic-Ischemic Encephalopathy

Changing Outcomes Across the Spectrum

Athina Pappas, MD[a], Gina Milano, MD[b], Lina F. Chalak, MD, MSCS[b,*]

KEYWORDS

• HIE • CP • Bayley • Hypothermia • Neurodevelopmental outcomes

KEY POINTS

- Therapeutic hypothermia significantly improves outcomes in hypoxic-ischemic encephalopathy (HIE), although infants with mild HIE are not well studied in trials.
- The loss of clinical equipoise regarding treatment of mild HIE is primarily due to overlapping definitions, a narrow therapeutic window for hypothermia and misclassifications during the early dynamic phase of encephalopathy.
- Standardizing the definition and cause of encephalopathy may help confirm HIE and exclude other causes.

INTRODUCTION

The prevalence of HIE is estimated at 0.5 to 1 per 1000 live births in the United States and developed nations and may be significantly higher in low-source and midresource settings where precise figures remain unknown but are likely higher.[1–3] Hypoxic-ischemic encephalopathy (HIE) is a form of neonatal encephalopathy that occurs in term and late-preterm neonates who have evidence of severe acidosis or need for resuscitation at birth followed by (1) direct evidence of an abnormal neurobehavioral state characterized by seizures or abnormalities in consciousness, tone, posture, and reflexes, (2) evidence of an acute perinatal or sentinel event, (3) characteristic neuroimaging findings, and (4) exclusion of other causes of neonatal encephalopathy. Meeting all the above criteria is not always feasible, particularly in the immediate postnatal period. Neonates with most of these findings often are treated with hypothermia as "presumptive HIE"—early recognition being paramount to the initiation of

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[a] Wayne Medical school, Detroit, MI, USA; [b] University of Texas Southwestern Medical Center, 5323 Harry Hines, Dallas, Texas 75390, USA
* Corresponding author.
E-mail address: Lina.chalak@utsouthwestern.edu

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neuroprotective therapies within a narrow therapeutic window. This review will focus on the spectrum of HIE, from mild to severe, and on the changing landscape of outcomes associated with therapeutic interventions. We will not address the other contributing causes of neonatal encephalopathy, which is beyond the scope of this article.

Pathophysiology

The pathophysiology of HIE is extrapolated from human neuropathological studies and from preclinical models with measurable hypoxic-ischemic insults (consisting of systemic hypoxemia, cerebral hypoperfusion, or both) that are characterized at the cellular level by a biphasic process of primary and secondary energy failure.[3,4] The initial phase consists of the triggering hypoxic-ischemic insult that leads to primary energy failure (a reduction in high-energy phosphorylated metabolites and intracellular pH). This phase may be so severe that it results in permanent brain injury or if subacute may be responsive to resuscitation and neuroprotective strategies. Approximately 6 to 24 hours later, secondary energy failure ensues characterized by the activation of proteases and endonucleases, neuronal apoptosis, microglial activation, reduction of growth factors and protein synthesis, and further accumulation of excitatory neurotransmitters. Neuronal cell death may be immediate or delayed and result from neuronal apoptosis or necrosis. In human neonates, the pathway to brain injury is not always clearly understood. Many factors such as the triggering event, the degree of brain maturation, the extent and timing of hypoxia-ischemia, the metabolic energy substrates, cerebral blood flow patterns, and the preinjury health status of the fetus can impact brain and multiorgan injury.[5] In addition, repetitive insults may contribute to more severe pathologic outcomes and brain injury than isolated insults.

Risk Factors. Risk factors contributing to the neurotoxic cascade that leads to HIE include a multitude of perinatal conditions associated with the need for neonatal resuscitation.[6,7] Perinatal events may fail to predict risk in some cases. Maternal factors associated with a higher risk of HIE include hypertension, cardiopulmonary abnormalities, hypovolemic or cardiovascular collapse, and status epilepticus among others. Uteroplacental factors include uterine rupture, placental abruption, infarction, fibrosis, underperfusion, and placenta previa. Umbilical cord factors include umbilical cord prolapse, cord entanglement or compression, a tight nuchal cord or a true knot in the cord, and abnormalities of umbilical vessels. Intrapartum and fetal factors include abnormal presentation, abnormal fetal heart rate monitor patterns, thick meconium, prolonged labor, precipitous delivery, outborn birth, difficult delivery requiring instrumentation (forceps, vacuum), prolonged pregnancy, fetomaternal hemorrhage, severe isoimmune hemolytic disease, arrhythmias, twin-to-twin transfusion syndrome, and others.

Identification of Neonates with Hypoxic-Ischemic Encephalopathy

Newborns with HIE present with characteristic signs and symptoms soon after birth that are characterized by physiologic and biochemical findings, neurologic examination abnormalities and electroencephalographic abnormalities. All neonates greater than 36 weeks' gestational age with a history of poor respiratory effort at birth and a need for resuscitation or evidence of neonatal encephalopathy should be carefully evaluated. The specific blood gas criteria that define HIE and are associated with neurologic compromise remain unknown.

Threshold blood gas criteria reported in trials to institute therapeutic hypothermia (TH) include the following: *pH* $\leq$ *7.0 or a base deficit of 16 mmol/L or more* in umbilical cord blood or any blood sample within the first hour of life[8–12] and *pH between 7.01*

and 7.15, base deficit 10 to 15.9 mmol/L within the first hour with any of the following: an *acute perinatal event*, a *10-minute Apgar score of 5 or lesser*, *assisted ventilation initiated at birth and continued for at least 10 minutes.*[9,13] *Neurologic examination findings* include seizures and evidence of neonatal encephalopathy (**Table 1**) or other signs of central nervous system dysfunction (eg, jitteriness, clonus, apnea, abnormal posturing, and movements).[14,15] Other clinical findings include clinical signs or symptoms of multiorgan injury. *Electroencephalographic findings* include electrographic seizures or abnormalities in background pattern, reactivity, organization of states, and maturation. In addition, amplitude integrated electroencephalogram (EEG) (aEEG) may reveal electrographic seizures or abnormalities in background pattern (discontinuous background, burst suppression, continuous low voltage, or flat/isoelectric background). The sensitivity of aEEG for identifying isolated seizures is poor[16,17]; short seizures, focal discharges, and low-amplitude seizures may not be detected.

The encephalopathy varies from mild to severe and is more likely a spectrum with overlap in the definition (see **Table 1**. Modified Sarnat criteria for the designation of HIE stage of encephalopathy).[14,15] Defining "mild HIE" is challenging because of the need to categorize the severity within the therapeutic window of 6 hours, despite the evolving nature of neonatal encephalopathy in the first week after birth and heterogeneity in the timing of the insult. Further adding to the complexity is the dynamic evolution of the disease process and clinical overlap of presenting signs as well as a lack of an accepted definition for what constitutes mild in the first 6 hours of life whereby decisions regarding therapies are made. Notably, the modified Sarnat Examination—the gold standard for staging HIE—did not distinguish between mild and normal status on the examination form for decades.[18]

The Prospective Research in Mild HIE (PRIME), an international multicenter observational cohort (NCT01747863) at 6 academic centers,[19] provides the first empirically validated definition of mild HIE within 6 hours using 2 steps, as in prior cooling trials: first, screening for fetal acidosis and acute perinatal events per neonatal institute of child health development (NICHD) criteria and second, a certified examination performed using a modified Sarnat scoring system, which is expanded to include mild in addition to the moderate and severe abnormalities (see **Table 1**). PRIME shows that a substantial proportion of infants with this definition of mild HIE have abnormal outcomes when treated without hypothermia. Specifically, 41% have abnormal neurologic findings at discharge, whereas 16% have a disability using established NICHD criteria and 40% have delays in cognitive and language development (<85 Bayley Scales of Infant Development [Bayley]-3 at 18–22 months).[20]

For moderate–severe HIE, medical management in the neonatal intensive care unit (NICU) includes supportive intensive care and hypothermia (whole body or selective head cooling with systemic hypothermia). For mild HIE, therapeutic interventions remain more controversial. However, recent reports suggest that treatment with TH have increased substantially; in a UK population study, 35.8% of newborns with mild HIE underwent cooling.[21] Optimization of TH and adjuvant therapies is under investigation.[22] Following stabilization and treatment of life-threatening conditions in the newborn period, physical, occupational, and developmental care should be initiated as soon as possible. Neonates with HIE should be enrolled in early intervention, follow-up and developmental care programs before discharge. Despite hypothermia to 33°C to 35°C for 72 hours, more than 40% of infants with HIE develop poor outcomes. In a recent meta-analysis of hypothermia trial data (of 1216 newborns), 26% of neonates offered hypothermia died, 26% developed major disability and 19% developed cerebral palsy at 18 to 24 months of age.[23] This has widespread

Table 1
Modified Sarnat criteria for designation of hypoxic-ischemic encephalopathy stage of encephalopathy

Categories	Normal	Mild	Moderate	Severe
Level of consciousness	Alert, responsive	Hyperalert, stare, exaggerated response to minimal stimuli, jitteriness, inconsolable	Lethargic	Stupor, coma
Spontaneous activity	Normal	Decreased, with or without periods of excessive activity	Decreased	No activity
Posture	Predominantly flexed when quiet	Mild flexion of distal joints (fingers, wrist)	Strong distal flexion, complete extension	Intermittent decerebration
Tone	Flexor tone in all extremities	Slightly increased peripheral tone	Hypotonia or hypertonia	Flaccid, rigid
Primitive Reflexes • Suck • Moro	Strong, easy to elicit Strong, easy to elicit	Weak, poor Low threshold to elicit	Weak or has bite Incomplete	Absent Absent
Autonomic nervous system • Pupils • Heart rate • Respirations	Normal size, reactive to light Normal heart rate Normal	Mydriasis Tachycardia (>160) Hyperventilation (>80)	Miosis Bradycardia (<100) Periodic breathing	Skew deviation/dilated, nonreactive/nonreactive Variable heart rate Apnea on ventilator with or without spontaneous respiration

Table 2
Two-year outcomes among survivors of hypoxic-ischemic encephalopathy in randomized control trials of hypothermia

Outcomes Among All Trial Participants									
	Death or Neurodevelopment Impairment (NDI)			Death			Major NDI (Among All)		
Study	N	Total	%	N	Total	%	N	Total	%
Gunn et al 1998[95]	7	18	39	3	18	17	4	18	22
Cool Cap Study 2005[11]	59	108	55	36	108	33	23	108	21
NICHD Study 2005[9]	45	102	44	24	102	24	21	102	21
TOBY Study 2009[8]	74	163	45	42	163	26	32	163	20
neo.nEURO Study 2010[10]	27	53	51	20	53	38	7	53	13
Zhou 2010[12]	31	100	31	20	100	20	11	100	11
ICE Study 2011[72]	55	107	51	27	108	25	28	107	26
All	298	651	**46**	172	652	**26**	126	651	**19**
Outcomes Among Survivors									
	Major NDI			MDI >2SD Below Mean			CP		
Study	N	Total	%	N	Total	%	N	Total	%
Gunn et al 1998[95]	4	15	27	3	13	23	3	15	20
Cool Cap Study 2005[11]	23	72	32	21	70	30	23	72	32
NICHD Study 2005[9]	21	78	27	19	75	25	15	77	19
TOBY Study 2009[8]	32	120	27	28	115	24	33	120	28
neo.nEURO Study 2010[10]	7	33	21				4	32	13
Zhou 2010[12]	11	80	14				10	80	13
ICE Study 2011[72]	28	80	35	17	73	23	21	79	27
All	126	478	**26**	88	346	**25**	109	475	**23**

implications for the children affected, their families, and the developmental care and assessment of these children at follow-up (Table 2).

Follow-up Care

All neonates with moderate–severe neonatal encephalopathy should undergo long-term follow-up because they are at heightened risk for poor outcomes including cerebral palsy, cognitive impairment, feeding issues, growth failure, postneonatal epilepsy, neurosensory impairment, and neuropsychiatric and behavioral problems.[24]

Cerebral Palsy Following Hypoxic-Ischemic Encephalopathy

Cerebral palsy is a term that describes a group of disorders characterized by abnormalities in muscle tone, movement, and/or posture associated with the loss of function presumed to be due to a nonprogressive lesion or abnormality in the developing fetal or infant brain.[25] Although a variety of perinatal risk factors (including HIE) are attributed to cerebral palsy (CP), in many cases, the true cause may be difficult if not impossible to ascertain.[7] Fewer than 10% of cases of cerebral palsy globally are attributable to HIE.[26] Nonetheless, cerebral palsy related to HIE has gained considerable attention because it may be amenable to postnatal therapies. In a meta-analysis of randomized

Table 3
Cerebral palsy among survivors of hypoxic-ischemic encephalopathy in randomized control trials of hypothermia

Trial	Hypothermia (%)	Normothermia (%)	Or (95% CI)
Cool Cap Study 2005[11]	32	43	0.75 (0.48–1.16)
NICHD Study 2005[9]	19	30	0.68 (0.38–1.22)
TOBY Study 2009[59]	28	41	0.67 (0.47–0.96)
Neo.nEURO Study 2010[10]	12	48	0.15 (0.04–0.60)
Zhou Study 2010[12]	14	28	0.40 (0.17–0.92)
ICE Study 2011[72]	27	29	0.92 (0.54–1.59)

controlled trials of hypothermia for HIE, 19% of neonates offered hypothermia developed disabling cerebral palsy at 18 to 24 months of age as compared with 31% of those treated with intensive care alone (**Table 3**).[23] Similar rates are reported at school age (17% and 29%, respectively).[27] Risk factors may include clinical variables (eg, initial severity and persistence of encephalopathy[28]) and other intrinsic factors (eg, genetic susceptibility, genetic polymorphisms[29]).

Two major CP subtypes are commonly associated with the mechanisms of HIE[7] (although other CP-subtypes are reported in the literature[30]). These include spastic quadriparesis (often observed following a watershed pattern of brain injury) and dyskinetic CP (often observed following injury to the basal ganglia, deep gray structures, and perirolandic cortex). Early detection may be feasible in high-risk infants using neonatal MRI,[31] neurologic examination, and the General Movements Assessment.[32–34] Definitive diagnosis typically is possible by 5 years (the age selected by CP registries to ensure diagnostic accuracy[35]). Presenting signs and symptoms may include abnormal muscle tone and deep tendon reflexes, gross motor developmental delay, abnormalities in postural or protective reflexes, and coordination of movement. Early detection allows for timely access to support services and early intervention.

Spastic cerebral palsy is characterized by increased or *spastic* passive tone of a clasp-knife character, increased deep tendon reflexes, pyramidal signs (eg, persistence of Babinski response) and sustained clonus.[25] Dyskinetic or athetoid cerebral palsy is characterized by spontaneous changes in muscle tone (dystonia), involuntary movements, and persistence of postural reflexes.[36] Other brain and nervous system symptoms may coexist. These include cognitive impairment, speech and language impairment, delays in developmental milestones, hearing or vision impairment and seizure disorders.[37] Orthopedic issues, contractures and dislocations of the hips and other joints may develop in severe cases, mainly between 3 and 6 years.[38]

Cerebral palsy may vary in severity from mild to severe; the risk of comorbidities increases with the extent of functional motor impairment.[39] Several developmental instruments may assist in grading the level of impairment such as the Gross Motor Function Classification System[25] and the Pediatric Evaluation of Disability Inventory.[40–42] Functional assessment tools for manual function and communication skills also exist (eg, Bimanual Fine Motor Function Scale, Manual Ability Classification System, Communication Function Classification System).[43,44]

Diagnosis is made by neurologic examination. Algorithms for the categorization of cerebral palsy may facilitate diagnosis (eg, the Surveillance for Cerebral Palsy in Europe Hierarchical Classification).[45,46] The following additional tests may be

performed: neuroimaging (preferably MRI of the brain), electroencephalogram, vision, and hearing testing. Management requires a team approach including a primary care physician; pediatric neurologist; neurodevelopmental specialist; physical medicine and rehabilitation physician; occupational, physical, and speech therapists; nurse; social workers; and other specialists (eg, gastroenterologist and/or orthopedic specialist). Prognosis varies depending on the severity of cerebral palsy and the response to therapeutic interventions aimed at minimizing functional impairment.[39] Cerebral palsy is a lifelong disorder that may require long-term care. Among children with CP following HIE, there is a high concordance between 18-month and 24-month level of functioning and school age outcomes.[27,47] Although there is no cure for cerebral palsy, treatment improves overall function, daily living and quality of life. Numerous effective interventions are available including casting, bimanual training, constraint-induced movement therapy, goal-directed training, hippotherapy, environmental enrichment, literacy interventions, oral stimulation, sensorimotor electrical stimulation, botulinum toxin, intrathecal baclofen, anticonvulsants, scoliosis correction, selective dorsal rhizotomy, and so forth.[48]

Cognitive Impairment Following Hypoxic-Ischemic Encephalopathy

Despite hypothermia and critical care management, cognitive impairment remains an acute and chronic problem for the survivors of neonatal encephalopathy. Greater than 50% of neonates with HIE have subnormal IQ scores (IQ < 85), and 27% have scores in the extremely low range (IQ < 70) even after hypothermia.[27] Cognitive deficits may exist with or without cerebral palsy or other neuromotor impairments.[49–51] Risk factors include severity of encephalopathy, poor head growth, neurologic comorbidities, parental IQ, environmental, and socioeconomic factors. Presenting signs and symptoms may include developmental delay, school difficulties, impaired memory and attention/executive function, lower school achievement, and special educational needs.[51,52] Cognitive impairment occurs over a spectrum ranging from mild learning disabilities to profound impairment.[27,53–55] Diagnosis is best achieved with formal testing using developmental instruments such as the Bayley, Griffith's Mental Development, NEPSY, or Wechsler intelligence scales. The spectrum of cognitive outcomes attributed to neonatal encephalopathy among infants treated with and without hypothermia is summarized in **Table 4**.

Management of cognitive impairment requires referral to early intervention (0–3 years) followed by school-based programs guided by an individualized educational plan.[56] Early therapy that includes the parents[57] and addresses the psychosocial needs of the child and family is paramount. Assistive devices may aid with communication and learning: glasses, hearing aids/cochlear implants, assistive communication devices, other adaptive equipment, and student or caregiver assistants.[58] These are vital to the optimal functioning of the child. Ongoing neurodevelopmental assessment, follow-up and intervention to address the special needs of children born with HIE, and any related comorbidities may positively affect outcomes. Prognosis depends on the severity of impairment and the presence of other comorbidities.[27,56] Severe cognitive impairment typically remains static throughout the life span.[27,47,59] Mild–moderate impairment without cerebral palsy or other neuropsychological comorbidities may be more amenable to therapeutic intervention; in these cases, cognitive scores observed in early infancy or childhood may improve with time (18–2 years vs school age).[60]

Cognitive Outcomes of Infants with Mild Hypoxic-Ischemic Encephalopathy

Definitions ascribed to mild HIE are not specific to the first 6 hours of age and use variable psychometric follow-up measures (**Table 5**). Studies reporting outcomes of

Table 4
Long-term cognitive and behavioral outcomes following moderate-to-severe hypoxic-ischemic encephalopathy

Author, Year	Study Type	Primary Outcome	Mean Age (Range)	Cohort Details	N	Sex (Boys/N)	Characteristic Controls	Measures	Results
Marlow et al,[51] 2005	Observational, case-control	Cognition and Behavior	7 y, 2 mo (6.5–9 y)	GA $\geq$ 35 wk, identified from the Trent Neonatal Survey database of babies born 1992–1994	65 participants, 50 without CP (N = 18 with severe NE)	31/50	N = 49 Children attending mainstream school were compared with a child from same school, matched for sex, age, ethnic group and first language	Cognitive BAS-II; NEPSY Behavior: SDQ (parental and teacher)	Cognitive outcomes: Moderate NE: No significant difference in general IQ or subscale scores on BAS; significantly lower scores on language, sensorimotor, narrative memory and sentence repetition domains on NEPSY Severe NE: Significantly lower scores compared with control group in general cognitive ability on BAS and multiple domains of NEPSY (attention, executive function, language, visuospatial, memory and learning, memory for names, narrative memory, orientation, and everyday memory) Behavioral outcomes: Moderate NE: no significant difference compared with control group. Severe NE: Significantly higher overall behavioral scores and hyperactivity compared with other comparison groups

Lindstrom et al,[96] 2006	Observational, cohort study	Cognition and Behavior	16 y, 1 mo (15–19 y 1, mo)	Term born Swedish cohort, born 1985	43 participants, 28 without CP	18/28	N = 15 siblings for comparison of behavior outcome	Cognitive (11/28): WISC-III Behavior (28/28): Parental questionnaires via telephone interview consisting of Connors 10-item scale, ADHD Rating Scale IV, Asperger Syndrome Screening Questionnaire	Cognitive outcomes: 4/11 with IQ $\leq$ 70; 3/11 with IQ 71–85 Behavioral outcomes: Significant differences compared with siblings on the Connors scale ($P < .003$), the inattention subscale of the ADHD Rating Scale IV ($P < .006$) and the Asperger Syndrome Screening Questionnaires
Steinman et al,[55] 2009	Observational, cohort study	Cognition	4 y		81 participants completed follow-up; 64 without neuromotor impairment	35/64 (55%)	NA	Cognitive: Wechsler Preschool and Primary Scale of Intelligence – Revised	Cognitive outcomes: Findings included an independent association between the degree of watershed injury on neonatal MRI and future verbal abilities measured by the WPPSI-R (11% with a verbal IQ score <70). There was no association between the degree of basal ganglia injury and verbal abilities

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Table 4
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Author, Year	Study Type	Primary Outcome	Mean Age (Range)	Cohort Details	N	Sex (Boys/N)	Characteristic Controls	Measures	Results
Van Kooij et al,[97] 2010	Observational, case-control	Cognition	9–10 y	Full-term infants born 1993–1997 and admitted to local NICU	80 survivors with mild or moderate NE. 69 children without CP	Unknown	52, matched for sex and age	Cognitive: WISC-III IQ estimated with subtests (Similarities, Vocabulary, Block Patterns, and Object Assembly)	Cognitive outcomes: control children had significantly higher mean estimate IQ scores as compared with the children with mild or moderate NE without CP. 17.4% of children without CP scored 1–2 SD less than the mean and 7.2% of children without CP scored less than 2 SD
Pappas 2015[98]	Observational, cohort study	Cognition and Behavior	6–7 y	School-aged survivors of the NICHD Neonatal Research Network RCT of whole body Hypothermia; participants were recruited between 2000 and 2003	110 participants, 86 without CP	61/110	NA	Cognitive: Wechsler intelligence scales, NEPSY Behavior: Parental report	Cognitive outcomes: Subnormal IQ scores were identified in more than a quarter of the children: 96% of survivors with CP had an IQ < 70, 9% of children without CP had an IQ < 70, and 31% had an IQ of 70–84. 20% of children with normal IQ and 28% of those with IQ scores 70–84 received special educational support services or were held back ≥1 grade Behavior outcomes: Behavior problems occurred in 21% of children at 18 mo (as

									indicated by the BSID-II Behavior Rating Scale) and 7% of children at 6–7 y of age (by parental report) among those treated with hypothermia
Van Schie et al,[99] 2015	Observational, cohort study	Behavior	7 y, 6 mo (6 y, 4 mo–8 y, 2 mo)	Born 1999–2002	25 participants, 17 without CP	19/25	NA	Behavior: Child Checklist (parents)	Behavior outcomes: 4/17 children had a total score in subclinical (n = 3) or clinical (n = 1) range; proportion not much higher than in reference sample
Hayes et al,[100] 2018	Observational, cohort study	Cognition and Behavior	5 y, 8 mo (3 y, 8 mo−8 y, 10 mo)	Born 2001–2005 retrospective data collection; 2005–2008 prospective assessments	68 participants without CP (N = 47 with mild HIE; N = 21 with moderate HIE)		NA	Cognitive: NEPSY-2 (58/68), Behavior Rating Inventory of Executive function (40/68) Behavior: Child Behavior Checklist (66/68)	Cognitive outcomes: Difficulties observed (>1 SD less than the mean) in 16/24 NEPSY-2 subtests and on timed assessments using Movement ABC-2. Abnormalities were observed in the "control" aspects of cognition (attention and memory) Behavior outcomes: Behavioral problems, particularly internalizing behaviors were higher than expected among survivors of HIE

Table 5
Characteristics of studies including mild hypoxic-ischemic encephalopathy not cooled

Author, Year	Center/Country/Dates	Number Mild HIE	Normal/ Abnormal Outcome	Inclusion Criteria	Outcome Definition	Follow-up mo/y	Standardized Follow-up Tools
Nadgyman et al, 2003	Berlin/Germany/1998–1999	14	10/4	37–42 wk GA Asphyxia	Mild = a DQ being 1–2 SD (91.8–97.8)	20 mo	Griffiths
Van Schie et al, 2015	Amsterdam/ Netherlands/1999–2002	6	4/2	38–42 wk GA Diagnosis of HIE I, II, or III	BSID-II Normal ≥85 Mild delay 70–84	7 y	M-ABC/CBCL Bayley@ 2 y
Liauw et al, 2009	Netherlands/2001–2003	3	2/1	>37 wk GA MRI to assess brain injury due to perinatal asphyxia	Category 3 + 4 = adverse	2 y and 5 y	Van Weichen Gessell and Towen
El-Ayouty et al, 2007	Mansoura/Egypt/2002–2004	3	3/0	38–42 wk GA Diagnosis of HIE I, II, or III	Abnormal = abnormal neurologic examination or Denver screening	18 mo	Denver Developmental Screen
Alderliesten et al, 2011	Utrecht/Netherlands/ 2002–2008	2	2/0	>36 wk GA Perinatal asphyxia, MRI, outcome	A composite death during the neonatal period, cerebral palsy, or Griffiths <85	18–46 mo	Griffiths
Murray et al, 2016	Cork/Ireland/2003–2005	22	16/6	≥37 wk GA Diagnosis of HIE I, II, or III EEG	Abnormal outcome at 5 y of age	5 y	WPPSI-III
Polat et al, 2013	Manisa/Turkey/2006–2008	11	10/1	37–41 wk GA Diagnosis of HIE I, II, or III		44–48 mo	Denver Developmental Screen
Gardiner et al, 2014	Perth/Australia/2008–2010	9	7/2	≥35 wk GA (mean 40 wk)<6 h old Asphyxia and or HIE II, III	Mild delay = 1 SD less than OR severe <2 SD	24 mo	Bayley-III

Looney et al, 2015	Cork/Ireland/2009–2011	15	9/6	>36 wk GA Perinatal asphyxia and HIE with matched controls	Abnormal outcome ≤85	18–36 mo	Bayley-III Ages and Stages (ASQ3)
Belet et al, 2004	Ankara/Turkey/Not reported	2	2/0	≥37 wk GA Diagnosis of HIE I, II, III	Bayley score and Denver score	3.5–4 y	Bayley Denver Developmental Screen
Lally et al, 2014	Kerala/India/Not reported	24	22/2	>36 wk GA encephalopathy who underwent MRI	Cerebral Palsy, or composite score <85	3.5 y	Bayley-III

infants treated for mild HIE are plagued by bias inherent to retrospective reports and a lack of systematic assessments after discharge.[61–68] Six studies conducted in Europe, 3 in Asia, 1 in Africa, and 1 in Australia have focused on mild HIE. All but one study provides infants intensive care alone without cooling. In the cooled non-RCT study 65 participants in total were enrolled, 9 had mild HIE and 2 (22%) had abnormal outcomes, the same percentage (22%) as in the noncooled outcome group. A meta-analysis including 558 participants, 111 of which had mild HIE, reports that 24 (22%) participants have abnormal outcomes at 18 months of age or older.[69]

Prehypothermia. Robertson and colleagues showed that no studied infants among those with mild HIE developed any major disability. The mean Stanford-Binet Intelligence Scale score was 101.5 (±14.0), and the mean developmental quotient using the Peabody Picture Vocabulary Test was 104.1 (±13.7)[70]; at 8 years of age, their school performance was similar to that of matched controls.[53] Subsequently, Van Handel and colleagues examined behavioral functioning at 9 to 10 years of age. Children with mild HIE had similar IQ compared with control children but social and attention problem scores were higher among the children with mild HIE.[71] Murray and colleagues evaluated cognitive outcomes at 5 years of age among 22 infants with mild HIE and reported that they had lower scores than control infants on full-scale IQ tests [99 (94–112) versus 117 (110–124), $P = .001$], verbal IQ [105 (99–111) versus 116 (112–125), $P = .001$], and performance IQ [103 (98–112) versus 115 (107–124), $P = .004$].[62] A systematic review summarized prehypothermia outcomes in a total of 250 mild HIE infants, with atypical results at greater than 18 months of age in 56 (22%).[63]

Outcome of Mild Hypoxic-Ischemic Encephalopathy in the Hypothermia Epochs

Four RCTs included infants with mild HIE due to their intent-to-treat analysis design.[63] Jacobs *and colleagues* enrolled 42 participants with mild HIE, and although not powered to examine the significance of the comparison, noted a rate of death or major sensorineural disability of 38% among those who received hypothermia versus 25% in those allocated to normothermia.[72] Zhou and colleagues[73] included 34 participants with mild HIE (19 hypothermia vs 15 control); abnormal outcomes were reported in 6/19 cooled and 7/15 controls. Battin *and colleagues*[74] enrolled 9 infants with mild HIE, abnormal outcomes occurred in 1/4 cooled and 2/2 controls. Wyatt and colleagues RCT[75] enrolled 8 infants with mild HIE and showed abnormal outcomes in 2/5 cooled and 0/3 in control. The pooled participants in these RCT studies were summarized in a recent systematic review, reporting an abnormal outcome in 29% of those receiving hypothermia versus 37% of controls, with an odds ratio of 0.67 (95% CI: 0.28–1.61, $P = .59$).[63] The trend was not significant and none of the studies were individually powered to detect a clinical effect of hypothermia for mild HIE.

Feeding Issues and Growth Failure

Feeding issues, dysphagia, and growth failure are common following HIE and may persist to school age.[76] Important risk factors include cranial nerve dysfunction leading to impaired swallowing, pharyngeal reflexes, and abnormalities in gastrointestinal motility.[77] Presenting signs and symptoms may include difficulty in sucking or swallowing, frequent choking, vomiting, aspiration, excessive drooling, and slower than normal growth.[78] In addition, irregular breathing, constipation, and urinary incontinence may be observed among severely affected children. Feeding issues may vary from absent to severe impairment requiring gastrostomy tube placement. Additionally, Nissen fundoplication may be required for children with severe gastroesophageal reflux.[79] Medical management should target both feeding issues and optimizing growth. Referral to occupational therapy, a registered dietitian or a specialized

multidisciplinary feeding clinic for a comprehensive evaluation and treatment plan is recommended.[80] The prognosis is child-dependent and is directly related to the severity of underlying hypoxic-ischemic brain injury.

Sleep and Altered Circadian Rhythm

In addition to neurodevelopmental impairment and growth failure, newborns with HIE are at risk for sleep-related circadian dysfunction that may further influence neurodevelopmental outcomes and family functioning; amplitude integrated aEEG may predict these abnormalities.[81]

Neonatal Seizures and Postnatal Epilepsy Following Hypoxic-Ischemic Encephalopathy

HIE is a common cause of seizures in the newborn period and beyond.[82] Whether seizures directly or indirectly contribute to brain injury among the survivors of HIE is controversial, due to the difficulty in separating the severity of the underlying brain injury from the impact of the seizures themselves. Treatment of seizures is also controversial. In a recent study by Hunt and colleagues, the treatment of electrographic and clinical seizures with commonly used antiepileptic drugs did not significantly improve outcomes beyond the neonatal period.[83] However, a study by Kharoshankaya and colleagues found an association between total neonatal seizure burden greater than 40 minutes with a more than 9-fold risk of abnormal neurodevelopmental outcomes (OR 9.56, 95% CI 2.43–37.67); this finding is independent of HIE severity at 6 hours, or of treatment with TH.[84] The presence of seizures alone is not associated with worse outcomes. TH decreases total seizure burden and has an antiepileptic effect.[85]

The incidence of repeated seizures beyond the newborn period is reported to be 10% to 16% at both 18 to 24 months[8,11] and 6 to 7 years of age.[27] Clinical presentation may vary from child to child in terms of severity and frequency of postnatal seizures. Seizures may lead to impaired control of muscle tone, movement, posture, thinking, speech, vision, gaze and/or bowel, and bladder function.[86] Postnatal seizures may range from none to intractable epilepsy (eg, infantile spasms)[87,88] and may be predicted by neuroimaging and neurophysiological measures (such as EEG and evoked potentials).[88] Early identification is critical to optimal management. Antiepileptic medications and close follow-up by a pediatric neurologist are recommended. The risk and benefit profiles of antiepileptic drugs used in this population are currently under investigation.[89,90]

Neuropsychiatric Comorbidities and Behavioral Problems

Children with a history of HIE are reported to have more special educational needs, memory and behavioral problems (see **Table 4**). Data are primarily from single center cohort studies of children treated with intensive care without hypothermia. One study reports severe behavioral problems in 8% of children with moderate HIE and 23% of children with severe HIE.[51] Another study reports more behavioral problems even among neonates with mild encephalopathy as compared with controls; children with mild or moderate encephalopathy manifest more social problems, anxiety, depression, attention deficit, autism symptomatology, and thought problems.[71] A few studies also suggest higher rates of hyperactivity among children with a history of moderate HIE.[51,71,91]

Neurosensory Impairment

Deafness occurs in 4% to 6% of children with moderate–severe HIE; blindness defined as (<20/200 vision) occurs in 6% to 14% of affected children.[8–12,23,72] Regular

assessment and prompt intervention for hearing and vision problems is important to the follow-up care of these children.

Parent and Family Well-Being

In children with neonatal encephalopathy due to HIE, parent mental health and social context are important contributing factors to cognitive and language functioning and neurodevelopmental outcomes.[92] Addressing the psychosocial needs of the family is an important part of follow-up care.

Involving families is essential and integral to the treatment care plan and to the long-term outcome of neonates affected by HIE.[93,94]

SUMMARY

Neonatal HIE is a leading cause of death and neurodevelopmental impairment in neonates. Standardizing the definition and cause of encephalopathy may help confirm HIE and exclude other causes. Understanding the stage and severity of encephalopathy and the long-term outcomes may affect treatment decisions and influence the choice to initiate TH. Traditionally, infants with mild HIE were treated with intensive care alone due to the perceived low risk for impairment. Recently, multiple studies suggest that infants treated for mild HIE without hypothermia may be at significant risk of abnormal neurodevelopmental outcomes. This review summarizes the spectrum of HIE presentations and their long-term implications.

Best practices

What is the current practice for defining HIE?

Newborns with HIE present with signs and symptoms soon after birth that are characterized by physiologic and biochemical findings, neurologic examination abnormalities and electroencephalographic abnormalities. Collectively, these criteria are used to define the stages of encephalopathy. Standardization of the definition of encephalopathy may help to confirm HIE and exclude other causes. This has implications on therapeutic interventions.

Best Practice/Guideline/Care Path Objective(s):

Presently, TH is the accepted best treatment modality for moderate–severe neonatal encephalopathy. Research is underway to determine whether TH may also benefit neonates with mild HIE. Challenges remain in defining mild HIE due to the need to categorize severity within the therapeutic window of 6 hours, the evolving nature of neonatal encephalopathy in the first week after birth and the heterogeneity in the timing of the insult. Further adding to the complexity is the dynamic disease process and clinical overlap of presenting signs, as well as a lack of an accepted definition for what constitutes mild in the first 6 hours of life whereby decisions regarding therapies are made.

What changes in current practice are likely to improve outcomes?

Clarification of the definition of HIE across the spectrum and further study of long-term outcomes is likely to improve the care of neonates with HIE.

Major Recommendations: Comprehensive follow-up care of neonates affected by HIE should include assessments of neuromotor outcomes, cognition, seizures neurosensory outcomes, behavior, sleep, growth, nutrition, functional impairment, and the influence on the family. Due to the high risk of potential adverse outcomes, follow-up should continue to school age and beyond.

Bibliographic Source(s): This is important: list current sources/references to support info above.

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