

Hypoxic-Ischemic Encephalopathy and Other Neonatal Encephalopathies

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REVIEW ARTICLE



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ABSTRACT

PURPOSE OF REVIEW: Neonatal encephalopathy is the most common condition in neonates encountered by child neurologists. The etiology is most often global hypoxia-ischemia due to failure of cerebral perfusion to the fetus caused by uterine, placental, or umbilical cord compromise prior to or during delivery. Other etiologies of neonatal encephalopathy include ischemic stroke and intracranial hemorrhage, infection, developmental anomalies, and inborn errors of metabolism.

RECENT FINDINGS: Therapeutic hypothermia is standard of care for the treatment of neonatal encephalopathy presumed to be caused by hypoxia-ischemia. The number needed to treat is approximately 6 to 7 to prevent one child from either death or disability at age 18 to 22 months. EEG monitoring and MRI are important tools in determining the etiology of encephalopathy and prognosis of the infant.

SUMMARY: Neonatal encephalopathy is a heterogeneous disorder that is characterized by alterations in mental status, hypotonia, seizures, and abnormalities in feeding and respiration. The most common cause of neonatal encephalopathy is hypoxic-ischemic encephalopathy, for which treatment with 72 hours of therapeutic hypothermia is associated with reduced death or disability.

INTRODUCTION

Neonatal encephalopathy is a heterogeneous condition that can be due to any disorder that disrupts the central nervous system in the first days of life. The characteristic signs of neonatal encephalopathy are altered mental status (eg, irritability, decreased responsiveness, coma), seizures, hypotonia, abnormal primitive reflexes, apnea, feeding disturbance, and abnormal cry.¹ Neonatal encephalopathy may be transient and reversible or may be the first sign of a brain injury, intracranial infection, or brain malformation that leads to a lifelong disability.

Neonatal encephalopathy that is caused by an intrapartum event leading to perinatal hypoxia-ischemia (sometimes called *perinatal asphyxia*) has historically been called *hypoxic-ischemic encephalopathy* (HIE); however, some prefer the term

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RELATIONSHIP DISCLOSURE:

Dr Glass has served on the editorial board of *Pediatric Neurology* and has given expert medical testimony related to medicolegal proceedings. Dr Glass receives research/grant support from the Cerebral Palsy Alliance, National Institutes of Health (grant numbers 1P01NS082330, 1UG3OD023272, and R03HD090298), Patient-Centered Outcomes Research Institute, and Pediatric Epilepsy Research Foundation.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Glass discusses the unlabeled/investigational use of fosphenytoin, levetiracetam, and phenobarbital for the treatment of neonatal seizure disorders.

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neonatal encephalopathy given that the exact pathogenesis is often not known.^{2,3} In this article, the term *neonatal encephalopathy* will be used as an umbrella term that encompasses HIE (or encephalopathy that is presumed to be caused by hypoxia-ischemia).

EPIDEMIOLOGY

The incidence of neonatal encephalopathy in the developed world is estimated at 2 to 6 per 1000 live term births, with HIE occurring in approximately 1.5 per 1000 live term births.⁴⁻⁶ Neonatal encephalopathy that is due to suspected or confirmed HIE is among the most common diagnoses encountered by a child neurologist and accounts for approximately 40% of new consults in the neonatal intensive care unit.^{7,8}

CLINICAL PRESENTATION

Clinical signs of encephalopathy include changes in consciousness and tone and depressed primitive reflexes as well as seizures. Sarnat and colleagues⁹ classified the severity of encephalopathy in the setting of presumed HIE as mild, moderate, or severe based on the worst degree of encephalopathy as observed on serial examinations. Importantly, the severity of encephalopathy is associated with mortality. Children with severe encephalopathy have a high rate of mortality, and survivors have a very high likelihood of permanent neurologic disability, whereas those with mild encephalopathy survive, and those with moderate encephalopathy have intermediate rates of death or disability.

ETIOLOGY

Neonatal encephalopathy may be due to a variety of conditions that can impair the central nervous system. While a well-defined hypoxic-ischemic event (eg, placental abruption, uterine rupture, cord prolapse) is the cause of encephalopathy in many infants, other causes of altered mental status or seizures in a neonate include ischemic or hemorrhagic stroke, infection, brain malformation, genetic conditions, and inborn errors of metabolism (TABLE 3-1¹⁰). Often, the exact etiology remains unexplained.

In many neonates with encephalopathy, the initial encephalopathy and seizures may resolve in the neonatal period. However, if the child has experienced a brain injury, neurologic deficits can emerge as the child ages.

EVALUATION OF THE NEONATE WITH ENCEPHALOPATHY

Since the etiology of encephalopathy is broad, a careful evaluation is warranted, especially in cases where the risk of perinatal asphyxia is low or where no sentinel event occurred.

History and Physical Examination

Maternal history should focus on an evaluation for antecedents of neonatal encephalopathy, including maternal medical history (eg, history of thromboembolic disorders and pregnancy loss) and use of medications or substance abuse, obstetric history (eg, results of prenatal screening and fetal ultrasounds), intrapartum events (including fetal heart rate monitoring), and placental pathology (to evaluate for placental abruption, vascular lesion, infection, or umbilical cord thrombosis). A family history of epilepsy and congenital neurologic and neuromuscular conditions may be a clue to a diagnosis other than HIE.

The infant's history must detail the onset, timing, and progression of encephalopathy and seizures. The presence of oliguria, hypotension, transaminitis, or coagulopathy suggests multiorgan failure and can support the occurrence of a global hypoxic event and a diagnosis of HIE.

In addition to a comprehensive neurologic examination, neonates should be carefully evaluated for signs of abnormal fetal development, including dysmorphic craniofacial features, birthmarks, and congenital anomalies of the internal organs and skeleton. A single or absent palmar crease, micrognathia, and joint contractures can indicate a long-standing decrease in fetal movements, suggesting prenatal onset of encephalopathy.

Laboratory Evaluation

Umbilical artery pH and base excess provide important clues regarding fetal perfusion. A comprehensive laboratory evaluation also includes newborn blood gas and lactate levels; a complete blood cell count, C-reactive protein, calcitonin, and blood cultures to look for signs of infection; glucose; electrolyte panel; tests for liver enzymes; creatinine and blood urea nitrogen; bilirubin levels; and a coagulation profile. If central nervous system infection is suspected, lumbar puncture should be performed for cell count, cultures, and viral studies (eg, herpes simplex virus, *Parechovirus*, and rotavirus, among others). In areas without a comprehensive newborn screen to test for inborn errors of metabolism or in cases where an inborn error of metabolism is suspected, additional evaluation including serum ammonia, serum amino acids, and urine organic acids may be warranted. Genetic evaluation, including single-nucleotide polymorphism array, is important to evaluate for the cause of congenital anomalies (including isolated brain malformations) and suspected syndromic diagnoses.

Neurophysiologic Monitoring

According to the American Clinical Neurophysiology Society, neurophysiologic brain monitoring using continuous video-EEG or, if continuous EEG is not available, an adapted montage and trending such as amplitude-integrated EEG is important to assess the degree of encephalopathy and recovery, as well as the presence of seizures.¹¹ Clinical evaluation alone without neuromonitoring can both overestimate and underestimate the burden of seizures. Clinical observation is unreliable, as movements that are not seizures may be interpreted as such by the bedside staff.^{12,13} In addition, neonates frequently have seizures without clinical correlate (subclinical seizures), and so seizures may go undetected or underrecognized in neonates who do not receive monitoring.^{14–16} Amplitude-integrated EEG is a limited channel recording that is displayed as a compressed tracing at the bedside (**FIGURE 3-1**).¹⁷ The advantage of this tool is that it is easy to apply and interpret by bedside nursing and medical staff. The primary disadvantage is that it has lower accuracy for seizure detection. Neurophysiologic brain monitoring should continue for at least 24 hours or until 24 hours after the last seizure.¹¹

Neuroimaging

MRI is recommended for all neonates with encephalopathy or seizures to assist with identifying the etiology of encephalopathy and to assist with prognosis. Head ultrasound is useful as a bedside tool to determine the presence of hemorrhage or ventriculomegaly; however, after a hypoxic-ischemic event,

KEY POINTS

- The hallmark signs of neonatal encephalopathy are altered mental status (eg, irritability, lethargy, coma), seizures, hypotonia, abnormal primitive reflexes, apnea, feeding disturbance, and abnormal cry.
- Neonatal encephalopathy that is caused by an intrapartum event leading to perinatal hypoxia-ischemia (sometimes called *perinatal asphyxia*) has historically been called *hypoxic-ischemic encephalopathy*; however, some prefer the term *neonatal encephalopathy* given that the exact pathogenesis is often not known.
- While a well-defined hypoxic-ischemic event (eg, placental abruption, uterine rupture, cord prolapse) is the cause of encephalopathy in many infants, other causes of altered mental status or seizures in a neonate include ischemic or hemorrhagic stroke, infection, brain malformation, genetic conditions, and inborn errors of metabolism.
- In addition to a comprehensive neurologic examination, neonates with encephalopathy should be carefully evaluated for signs of abnormal fetal development, including dysmorphic craniofacial features, birthmarks, and congenital anomalies of the internal organs and skeleton.

head ultrasound is often normal in the acute setting.¹⁸ CT is rarely used in infants because of the need for high radiation doses to achieve adequate resolution of brain parenchyma.

MRI can be performed safely (and often without sedation) in critically ill children with appropriate monitoring and training. In addition to conventional imaging (T1- and T2-weighted MRI), diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy are important to identify acute injury, whereas susceptibility-weighted imaging (SWI) can improve identification of small areas

TABLE 3-1

Differential Diagnosis of a Neonate With Altered Mental Status or Seizures

Hyoxic-Ischemic Encephalopathy (Global Hypoxia-Ischemia)

- ◆ Sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery (eg, placental abruption, uterine rupture, cord prolapse)
- ◆ Heart rate monitor patterns consistent with an acute peripartum or intrapartum event
- ◆ Apgar score of less than 5 at 5 minutes and 10 minutes
- ◆ Fetal umbilical artery pH of less than 7.0 or base deficit of 12 mmol/L or greater
- ◆ Onset of encephalopathy within the first 24 hours of life
- ◆ Presence of multiorgan failure consistent with hypoxia-ischemia (eg, elevated transaminases, hypotension/cardiomyopathy, renal failure, bone marrow failure)

Bacterial or Viral Sepsis or Intracranial Infection

- ◆ Set up for infection (eg, prolonged rupture of membranes, maternal fever, and chorioamnionitis)
- ◆ Mother positive for group B streptococcus
- ◆ Temperature instability
- ◆ Apnea/bradycardia
- ◆ Hypotension
- ◆ Hepatic dysfunction including hyperbilirubinemia
- ◆ Disseminated intravascular coagulopathy

Ischemic Perinatal Stroke

- ◆ Neonate who appears otherwise healthy with focal motor seizures is the most common clinical presentation
- ◆ Focal arterial ischemia on MRI

Intracranial Hemorrhage

- ◆ Small subdural hemorrhages are rarely symptomatic
- ◆ Intraventricular hemorrhage and periventricular or cerebellar hemorrhages due to fragile germinal matrix are a common cause of encephalopathy and seizures in preterm neonates
- ◆ Intraventricular hemorrhage/thalamic hemorrhage in a term neonate should prompt search for cerebral sinovenous thrombosis
- ◆ Parenchymal hemorrhages in a term neonate may be due to sinovenous thrombosis, trauma, coagulopathy, vascular malformation, or genetic cause (eg, collagen type IV alpha 1 chain [COL4A1] mutation), although the cause is often not found

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of hemorrhage. Conventional T1 and T2 images must be evaluated for structural developmental malformations, as these lesions may cause early encephalopathy or seizures and may also predispose to secondary hypoxic-ischemic injury during the birth process.¹⁹ DWI can be used to detect anatomic areas of injury in the acute phase (approximately the first 7 to 10 days after injury). Magnetic resonance spectroscopy may show a lactate peak (a sign of abnormal metabolism most often due to acute injury) or low *N*-acetylaspartate (NAA) (indicating decreased neuronal integrity).

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Brain Malformation

- ◆ Abnormal fetal or neonatal ultrasound or MRI
- ◆ Associated craniofacial dysmorphisms or organ anomalies
- ◆ Genetic abnormality

Inborn Error of Metabolism

- ◆ Cerebral edema or symmetric pattern of injury
- ◆ Persistent lactic acidosis
- ◆ High ammonia
- ◆ Feeding intolerance/vomiting
- ◆ Unusual odor

Neonatal-Onset Epileptic Encephalopathy

- ◆ Persistent clinical and/or EEG seizures despite medication escalation
- ◆ Prominent tonic symptomatology
- ◆ EEG with persistent burst suppression
- ◆ Worsening clinical status or EEG patterns
- ◆ MRI in the first week of life without acute injury
- ◆ Gene mutation (eg, *KCNQ2*, *KCNQ3*, *SCN1A*, *SCN2A*, *SLC13A5*, *STXBPI*, *KCNT2*, *GDLC*, *CDKL5*, *CHD7*)¹⁰

Transient Encephalopathy

- ◆ Maternal use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), drugs of abuse
- ◆ Electrolyte abnormality
- ◆ Hypoglycemia

EEG = electroencephalogram; MRI = magnetic resonance imaging.

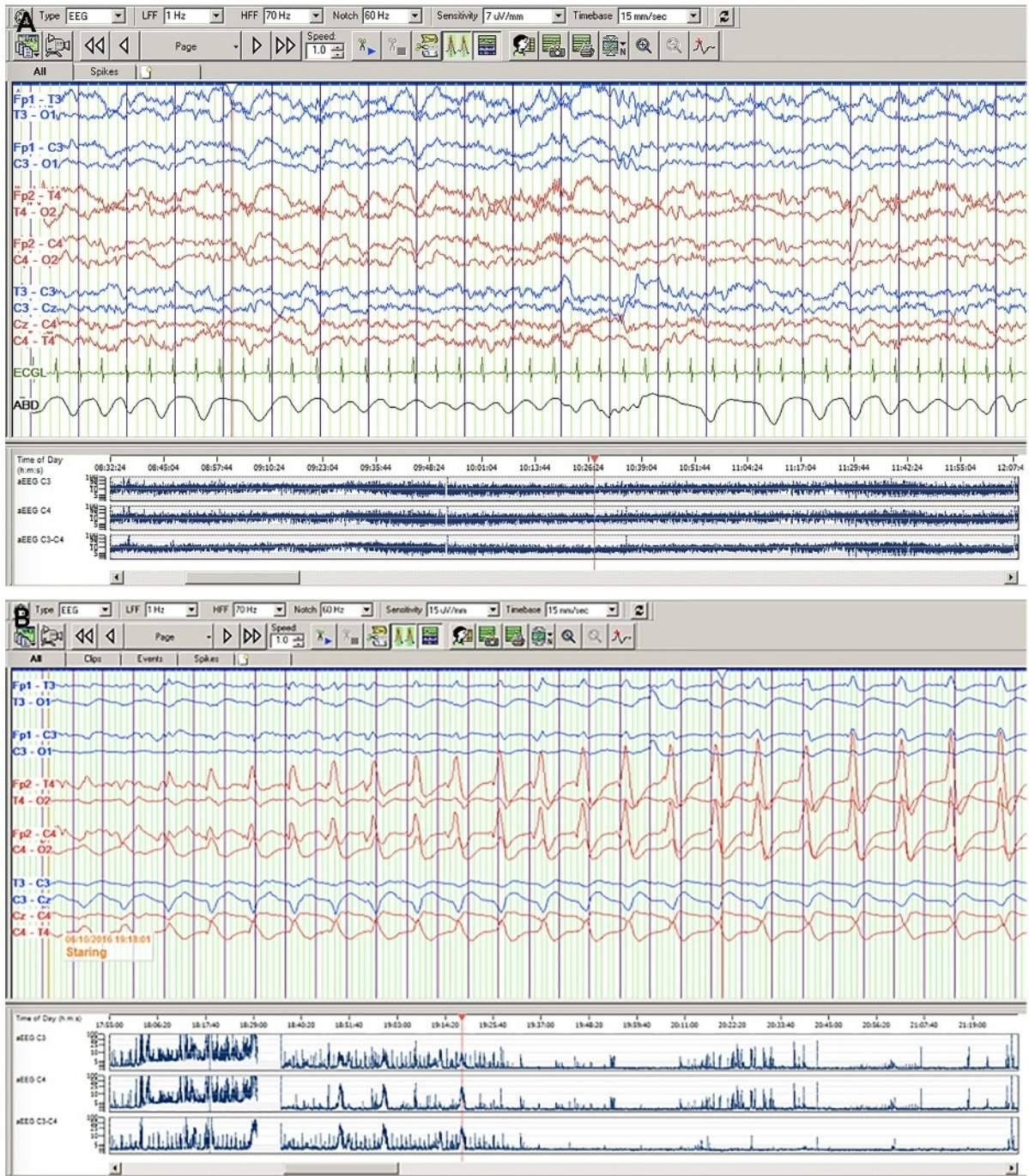


FIGURE 3-1

Concurrent EEG and amplitude-integrated EEG in two neonates with presumed hypoxic-ischemic encephalopathy. Neonatal EEG montage is displayed at 15 mm/sec and with sensitivity of 7 μ V/mm (A) and 15 μ V/mm (B). Amplitude-integrated EEG time scale is noted with each compressed trace, representing more than 3 hours of recording. A, Upper panel of normal continuous EEG and amplitude-integrated EEG shows normal continuous voltage with cycling in a neonate with encephalopathy presumed to be caused by hypoxic-ischemic encephalopathy who is status post-therapeutic hypothermia. B, Lower panel showing neonate with encephalopathy presumed due to be caused by hypoxic-ischemic encephalopathy. The seizure arising from T4 on the EEG is evident as a sudden rise in the lower and upper margins of the suppressed amplitude-integrated EEG.

MRI is an important prognostic tool, as the pattern and severity of injury are helpful in predicting later deficits. For neonates who receive therapeutic hypothermia, the burden of injury apparent on MRI is lower, particularly in basal ganglia and thalamus but also in the white matter and watershed regions.^{20–22}

MANAGEMENT OF THE ENCEPHALOPATHIC NEONATE

Neonates with encephalopathy should be cared for in a neonatal intensive care unit with capacity to provide neuromonitoring, neuroimaging, and subspecialty neurologic care.

Neurocritical Care

Advances in basic cardiopulmonary support, favorable evidence from the adult neurocritical care literature, and improved understanding of the impact of critical illness on the developing brain have led to the emergence of neonatal neurocritical care (also called neonatal neurointensive or brain-focused care) as an important approach that can potentially improve developmental outcomes in neonates with encephalopathy.²³ The focus of neonatal neurocritical care involves a culture change for the entire neonatal intensive care unit toward brain-focused care, such that all care providers are continually aware of the neurologic implications of critical illnesses and the impact of management strategies on the developing brain.^{24,25} For example, optimized care involves active management of temperature (including therapeutic hypothermia for neonates with encephalopathy due to hypoxia-ischemia and avoiding hyperthermia for all brain-injured neonates),²⁶ blood pressure (to avoid fluctuations in brain perfusion in the setting of critical illness and pressure passive circulation), oxygenation/ventilation, and glucose (especially avoiding hypoglycemia, which can cause de novo injury and may exacerbate underlying hypoxic-ischemic injury).^{27–29} This attention to physiologic homeostasis is especially important during resuscitation and the so-called “golden” first hour after delivery.³⁰

In addition to medical management, application of advanced technologies such as digital EEG with bedside trending (such as amplitude-integrated EEG) and remote review allow bedside assessment of brain function in real time. Furthermore, safe, high-resolution brain imaging using MRI is widely available as an important tool to assess the impact of critical illness on brain structure and development.

A focus on the brain during the period of critical illness allows for medical interventions, including application of therapeutic hypothermia and treatment of seizures in real time, developmentally supportive care, compassionate communication with families, and, if appropriate, early decision making regarding goals of care. According to the literature on acute brain injury in adults, a neurocritical care approach leads to higher rates of favorable outcomes by the following mechanisms: (1) earlier recognition and treatment of neurologic conditions; (2) prevention of secondary brain injury through attention to maintenance of physiologic homeostasis of factors such as temperature, blood pressure, and glucose; (3) consistent management using guidelines and protocols; and (4) use of experienced specialized teams at dedicated referral centers.³¹

Therapeutic Hypothermia for Neonatal Encephalopathy

Therapeutic hypothermia to 33.5°C (92.3°F) for 72 hours is standard of care for neonates at least 36 weeks gestational age at birth who have neonatal encephalopathy that is due to suspected or confirmed hypoxia-ischemia.³² The

KEY POINTS

- The American Clinical Neurophysiology Society recommends neurophysiologic monitoring using continuous EEG or amplitude-integrated EEG to determine the presence of electrographic seizures and to establish the severity of encephalopathy.

- MRI is recommended for all neonates with encephalopathy or seizures to assist with identifying the etiology of encephalopathy, as well as for assisting with prognosis.

- Optimized care involves active management of temperature (including therapeutic hypothermia for neonates with encephalopathy due to hypoxia-ischemia and avoiding hyperthermia for all brain-injured neonates), oxygenation/ventilation, and glucose (especially avoiding hypoglycemia, which can cause de novo injury and may exacerbate underlying hypoxic-ischemic injury).

- Therapeutic hypothermia to 33.5°C (92.3°F) for 72 hours is standard of care for neonates who are at least 36 weeks gestational age and who have neonatal encephalopathy that is due to suspected or confirmed hypoxia-ischemia.

proposed mechanisms of neuroprotection by hypothermia include suppression of apoptosis, reduced inflammation and cytotoxic edema, lowered cerebral metabolism, and modulation of seizure severity.³³ Several randomized controlled trials and meta-analyses demonstrated reduced death or disability at 18 to 24 months of age (relative risk 0.75, 95% confidence interval, 0.68–0.83), a higher number of children with a normal outcome, and sustained benefits to children from infancy until they reach school age (although loss to follow-up has been a significant issue in the large trials).^{34–36} The number needed to treat to prevent death or disability is, on average, about 6 to 7. A trial of longer (120 hours) or deeper (32.0°C [89.6°F]) cooling was terminated early when a futility analysis determined that the likelihood of benefit of longer or deeper cooling (or both) for neonatal death was less than 2%.³⁷

Eligibility criteria varied slightly between the clinical trials and typically involved some combination of gestational age (generally 36 weeks or more, although one study cooled neonates at 35 weeks), indicator of perinatal distress (an Apgar score of less than 5 at 10 minutes, blood gas pH of less than 7.00 or base excess of –12 mmol/L to –16 mmol/L or more from the umbilical cord or within the first hour of life, or more than 10 minutes of resuscitation), and moderate to severe encephalopathy. Some regional systems have implemented screening criteria for when to call a cooling center to improve identification of eligible neonates.

Therapeutic hypothermia should be implemented within 6 hours after birth, and evidence from preclinical studies and the randomized controlled trials suggests that earlier implementation leads to lower rates of death or moderate/severe disability.^{38–40} Disability is variably defined depending on the trial and is typically some combination of low scores on standardized cognitive testing, functionally disabling cerebral palsy, epilepsy, and vision or hearing impairment.⁴¹

Passive cooling can be safely initiated prior to transport; servo-controlled devices that help to maintain stable temperature and avoid overcooling are available for use during transport.⁴² Both head cooling and whole-body cooling appear equally effective.³⁴ Whole-body cooling has been preferentially adopted due to the ready availability of cooling blankets at many centers, as well as better access to the infant's head for brain monitoring using EEG. Many centers use sedation (eg, with morphine sulfate) to prevent discomfort, cold stress, and shivering.

Continuous brain monitoring, preferably with continuous video-EEG, is recommended for all neonates undergoing hypothermia.⁴¹ The risk of seizures in neonates undergoing hypothermia is approximately 50%.^{43–45} Seizures most commonly arise within the first 24 hours of life and should be treated as rapidly as possible after detection using adequate doses of antiseizure medications. Phenobarbital (20 mg/kg initial dose) and phenytoin (or preferably fosphenytoin at 20 mg/kg of phenytoin equivalents) have similar efficacy; however, approximately one-half of children have recurrent seizures after the initial bolus of either medication.⁴⁶ Levetiracetam is also used to treat seizures in neonates (40 mg/kg to 60 mg/kg initial dose); however, limited data exist regarding efficacy. In the case of recurrent seizures, escalating doses of antiseizure medications are warranted to abolish electrographic seizures (including those without clinical correlate). Recurrent (or rebound) seizures have been reported during the rewarming phase of therapeutic hypothermia, although this phenomenon appears to be relatively uncommon.⁴⁷ In the setting of acute symptomatic seizures due to HIE, prolonged treatment is rarely warranted. Although limited evidence exists to guide duration

of treatment, in almost all cases, antiseizure medications can safely be discontinued once the acute symptomatic seizures have resolved.^{48,49}

EEG is prognostic for brain injury and developmental outcomes in neonates undergoing hypothermia. Normal or mildly abnormal EEG (eg, mild excess discontinuity) or early recovery from severe abnormalities within the first 24 to 36 hours after birth portends good prognosis, whereas severe (and especially persistently severe) abnormalities (eg, burst suppression, depressed and undifferentiated tracing, extremely low voltage) are associated with moderate to severe brain injury, death, and disability.⁵⁰⁻⁵²

MRI is recommended for all neonates undergoing hypothermia to assist with determining etiology of encephalopathy, timing of injury, and prognosis. The predominant patterns of injury in neonates with HIE are (1) basal ganglia/thalamus (with extension to rolandic cortex, hippocampus, and brainstem in severe cases), which is seen predominantly in the setting of acute profound disruption in placental perfusion **FIGURE 3-2**, and (2) watershed areas (with injury to the watershed zones of the anterior, middle, and posterior cerebral arteries), which occurs in the setting of partial prolonged disruption of placental perfusion (**CASE 3-1** and **CASE 3-2**).⁵³

Hypothermia is associated with reduced extent of injury on MRI, especially injury to the thalamus and basal ganglia.^{20,21} MRI is useful to ensure that the diagnosis of HIE is, in fact, correct given that children with underlying anomalies are at higher risk for peripartum asphyxia and imaging may reveal unexpected findings such as brain malformations.^{19,54} In addition, the MRI provides useful prognostic information (**TABLE 3-2**⁵⁵⁻⁶⁰).^{20,59} Children with injury to the thalamus or basal ganglia typically develop cerebral palsy, whereas outcome for children with the watershed pattern of injury is variable, and outcome may be favorable even in children with severe injury.^{57,60}

Alternative and Adjuvant Neuroprotective Agents

Multiple alternative and adjuvant agents that target various mechanisms in the cascade of events that lead to neuronal necrosis and apoptosis are under investigation in preclinical and clinical studies.^{61,62} Examples of target mechanisms and agents include (1) preventing free radical-induced injury (eg, antioxidants such as melatonin, allopurinol, and *N*-acetylcysteine), (2) reducing excitotoxicity (eg, xenon, magnesium sulfate, cannabinoids), (3) anti-inflammation, and

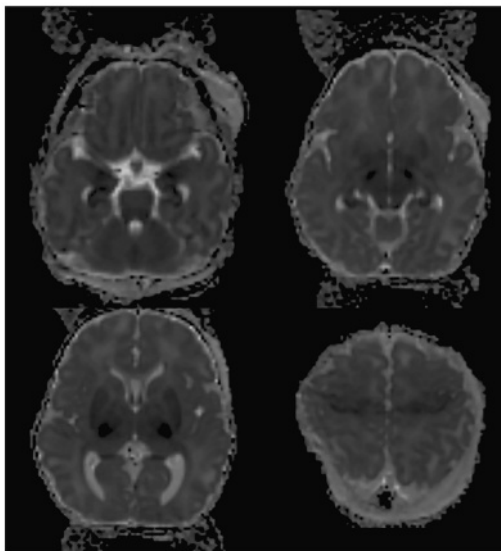


FIGURE 3-2 Apparent diffusion coefficient map on the fourth day after birth in a full-term neonate born by cesarean delivery after maternal uterine rupture shows reduced diffusion in the ventrolateral thalamus, basal ganglia, motor cortex, hippocampus, and brainstem.

KEY POINTS

- Eligibility criteria in clinical trials for therapeutic hypothermia for neonatal encephalopathy varied slightly between trials and typically involved some combination of gestational age, indicator of perinatal distress, and moderate to severe encephalopathy.
- Therapeutic hypothermia should be implemented within 6 hours after birth, and evidence from preclinical studies and the randomized controlled trials suggests that earlier implementation leads to better outcomes.
- Continuous brain monitoring, preferably with continuous video-EEG, is recommended for all neonates undergoing hypothermia.
- The risk of seizures in neonates undergoing hypothermia is approximately 50%.
- Normal or mildly abnormal EEG (eg, mild excess discontinuity) or early recovery of severe abnormalities within the first 24 to 48 hours after birth portends good prognosis, whereas severe (and especially persistently severe) abnormalities (eg, burst suppression, depressed and undifferentiated tracing, extremely low voltage) are associated with brain injury, death, and disability.

(4) repair and regeneration (eg, erythropoietin, stem cells). These agents are currently being evaluated in preclinical or clinical trials and are not in widespread clinical use.

Prognosis

Neonates with encephalopathy are at risk for long-term disabilities, including cerebral palsy, epilepsy, and cognitive impairment. The predictors of unfavorable outcomes are indicated in **TABLE 3-2**. Therapeutic hypothermia does not prevent adverse outcomes in all patients. The rate of death or disabilities in the randomized controlled trials was approximately 50%.⁶³ Similarly, the rates of cerebral palsy and developmental delay are lower among cooled neonates; however, they remain approximately 19% for cerebral palsy and 23% for developmental delay.

CASE 3-1

An infant girl was born at 39 weeks gestation by emergent cesarean delivery due to maternal placental abruption. Apgar scores were assigned as 0 at 1 minute, 2 at 5 minutes, 2 at 10 minutes, and 5 at 15 minutes. Cord arterial pH was 6.90 with base deficit 17 mmol/L. The initial neurologic examination 60 minutes after birth was remarkable for decreased responsiveness, absent suck/gag, generalized hypotonia, and stereotyped response to noxious stimuli.

Therapeutic hypothermia was initiated for treatment of suspected hypoxic-ischemic encephalopathy (HIE) due to placental abruption. The target temperature was achieved by 2 hours after birth. The initial EEG was discontinuous with interburst intervals of up to 17 seconds and without obvious state changes. Fourteen hours after birth, the infant experienced four focal seizures lasting 45 to 60 seconds each that stopped following a single dose of IV phenobarbital (20 mg/kg).

By the day after birth, the infant had spontaneous eye opening and was more responsive. The EEG had improved, showing only mild excess discontinuity with interburst intervals of up to 8 seconds during sleep. Phenobarbital was discontinued. MRI performed the fourth day after birth was normal, including diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy with a voxel placed in the left basal ganglia. The child was taking full oral feeds via breast-feeding by the fifth day after birth and was discharged home on the seventh day after showing adequate oral intake. Prior to discharge home, the parents were counseled regarding a cautiously optimistic prognosis based on early improvement of EEG and neurologic examination as well as the normal MRI. At age 2, the child had normal development and had not had recurrent seizures.

COMMENT

This case demonstrates the importance of implementing therapeutic hypothermia at the earliest possible time after recognition of HIE. This case also demonstrates the prognostic value of early improvement of the EEG and of normal MRI, as well as the possibility of good outcomes after HIE even in children with severe acidosis and low Apgar scores.

Reasons for absent or incomplete effect of hypothermia may be delayed onset of cooling, injury that is too severe, or incorrect diagnosis.

MANAGEMENT OF ENCEPHALOPATHY NOT DUE TO HYPOXIC-ISCHEMIC ENCEPHALOPATHY

If HIE is not the cause of the encephalopathy, then the general neurocritical care principles discussed above (eg, maintaining normal glucose, temperature, blood pressure) apply; however, therapeutic hypothermia is not indicated. Neonates with suspected infection as the cause of encephalopathy should be treated with antimicrobial agents (or antiviral agents if herpes simplex virus is suspected). Neonates with arterial stroke should have a careful cardiac examination to assess for congenital heart defects and a family history taken to assess for risk factors for thrombophilia. Neonates with bland or hemorrhagic venous infarcts should be reimaged within 1 week and consideration given for anticoagulation if an acute clot is identified.^{64,65} In the setting of neonatal encephalopathy due to brain malformation, a suspected or confirmed inborn error of metabolism, or neonatal-onset epileptic encephalopathy, a specific genetic diagnosis should be sought.

KEY POINT

- The predominant patterns of injury in neonates with hypoxic-ischemic encephalopathy are (1) basal ganglia/thalamus (with extension to rolandic cortex, hippocampus, and brainstem in severe cases, which is seen predominantly in the setting of acute profound disruption in placental perfusion), and (2) watershed areas (with injury to the watershed zones of the anterior, middle, and posterior cerebral arteries), which occurs in the setting of partial prolonged injuries.

A 37-year-old woman with gestational diabetes mellitus and hypertension who was pregnant with a 41-week-gestation male fetus presented to obstetric triage because of decreased fetal movements during the previous 12 hours. Labor was induced, and after 24 hours of induction, the fetal heart monitor showed bradycardia to 60 beats/min, and the child was delivered emergently by cesarean delivery. The child was limp, apneic, and bradycardic at birth. Apgar scores were assigned as 1 at 1 minute, 2 at 5 minutes, and 4 at 10 minutes. The child was intubated and transferred to a regional cooling center. During transport, the child had several episodes of asymmetric tonic stiffening with changes in vital signs and was treated with 20 mg/kg of IV phenobarbital followed by maintenance dosing for presumed seizures.

CASE 3-2

Cooling was initiated at 5 hours after birth. EEG initiated at 10 hours after birth showed status epilepticus without clinical correlate. The child received an additional 20 mg/kg of phenobarbital, after which he was unresponsive, and the background EEG pattern showed no definite cerebral activity. This EEG pattern persisted throughout cooling and rewarming. An MRI on the fifth day after birth showed injury to the thalamus, basal ganglia, and much of the cerebral cortex and subcortical white matter. Magnetic resonance spectroscopy showed a large lactate peak and low *N*-acetylaspartate (NAA) in the basal ganglia. The parents were counseled regarding expected poor prognosis, and they chose to discontinue life support and provide the child with palliative care.

This case exemplifies several key indicators of a poor prognosis in neonates with hypoxic-ischemic encephalopathy: status epilepticus, persistently severely abnormal EEG, and severe injury on MRI.

COMMENT

KEY POINTS

- Developmental care by occupational and physical therapists and lactation experts can begin during the inpatient admission to assess and manage positioning, oral feeding readiness and preparation, and behavioral state regulation and to optimize tone, strength, and ability to deal with environmental stimuli.
- Since survivors of neonatal encephalopathy are at high risk for long-term disabilities, children should be followed longitudinally by a high-risk program or a child neurologist as recommended by the American Academy of Pediatrics.

LONG-TERM MANAGEMENT

Once the neonate with encephalopathy has recovered from the critical illness, the focus turns toward establishing oral feeding and readiness for discharge home. Developmental care by occupational and physical therapists and lactation experts can begin during the inpatient admission to assess and manage positioning, oral feeding readiness and preparation, and behavioral state regulation and to optimize tone, strength, and ability to deal with environmental stimuli.²⁴ Developmentally appropriate exercises (eg, upright positioning, “tummy time,” language exposure, and early exposure to fine motor tasks) can be initiated in the hospital and taught to the parents for practice at home.

Since survivors of neonatal encephalopathy are at high risk for long-term disabilities, children should be followed longitudinally by a high-risk program or a child neurologist as recommended by the American Academy of Pediatrics.³² Close monitoring ensures appropriate and timely referrals to developmental therapies such as occupational and physical therapy. Follow-up should be at least until 18 to 24 months of age; however, follow-up until school age is preferred.

CONCLUSION

Neonatal encephalopathy is a heterogeneous disorder marked by altered mental status, altered muscle tone, and depressed primitive reflexes, as well as seizures. Therapeutic hypothermia is standard of care for neonates with encephalopathy that is presumed to be caused by hypoxia-ischemia and who would have fulfilled entry criteria into the large randomized trials. Brain-focused

TABLE 3-2 Predictors of Outcome in Neonates Treated With Therapeutic Hypothermia

	Indicators of Poor Prognosis	Indicators of Good Prognosis
Clinical examination	Unresponsive, minimally responsive, or stereotyped responsiveness persisting beyond 24–36 hours after birth	No or mild encephalopathy at 24 hours ⁵⁵
EEG/amplitude-integrated EEG	Severe abnormality (burst suppression, depressed and undifferentiated tracing, extremely low voltage on continuous EEG; burst suppression or flat tracing on amplitude-integrated EEG), especially if it persists beyond 24–36 hours after birth ^{50–52} Seizures that are refractory to initial loading doses of antiseizure medications or multifocal ⁵⁶	Early normalization of EEG/ amplitude-integrated EEG (within 24–36 hours) Early return of sleep-wake cycling Seizures that respond to first-line medication
MRI	Moderate to severe injury (and especially near-total injury) Injury to the ventrolateral thalamus or basal ganglia ⁵⁷ Absent myelination of the posterior limb of the internal capsule ⁵⁸ Magnetic resonance spectroscopy lactate: <i>N</i> -acetylaspartate that is greater than 1/3 ⁵⁹	Children with focal or watershed pattern of injury, even with high injury burden, may have a favorable outcome ⁶⁰

EEG = electroencephalogram; MRI = magnetic resonance imaging.

management includes neurophysiologic monitoring and imaging with MRI to help determine diagnosis, prognosis, and neurologic complications, as well as careful attention to maintenance of normal homeostatic mechanisms (eg, glucose, blood pressure) to help prevent secondary brain injury. While outcomes have improved since the widespread use of hypothermia, risk of death or disability in the clinical trials was almost 50%. Emerging adjuvant therapies such as erythropoietin hold promise for further improving outcomes.

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