

Neonatal Encephalopathy: Beyond Hypoxic-Ischemic Encephalopathy

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Practice Gaps

1. Hypoxic-ischemic encephalopathy (HIE) is the most common cause of neonatal encephalopathy; however, clinicians should recognize other etiologic factors and understand when to pursue additional evaluation.
2. Evaluation for neonatal encephalopathy should always include laboratory studies on blood, urine, and cerebrospinal fluid, as well as brain imaging and electroencephalography.
3. There is overlap among the different causes of neonatal encephalopathy.

Abstract

Neonatal encephalopathy is a clinical syndrome of neurologic dysfunction that encompasses a broad spectrum of symptoms and severity, from mild irritability and feeding difficulties to coma and seizures. It is vital for providers to understand that the term “neonatal encephalopathy” is simply a description of the neonate’s neurologic status that is agnostic to the underlying etiology. Unfortunately, hypoxic-ischemic encephalopathy (HIE) has become common vernacular to describe any neonate with encephalopathy, but this can be misleading. The term should not be used unless there is evidence of perinatal asphyxia as the primary cause of encephalopathy. HIE is a common cause of neonatal encephalopathy; the differential diagnosis also includes conditions with infectious, vascular, epileptic, genetic/congenital, metabolic, and toxic causes. Because neonatal encephalopathy is estimated to affect 2 to 6 per 1,000 term births, of which HIE accounts for approximately 1.5 per 1,000 term births, (1)(2)(3)(4)(5)(6) neonatologists and child neurologists should familiarize themselves with the evaluation, diagnosis, and treatment of the diverse causes of neonatal encephalopathy. This review begins by discussing HIE, but also helps practitioners extend the differential to consider the broad array of other causes of neonatal encephalopathy, emphasizing the epidemiology, neurologic presentations, diagnostics, imaging findings, and therapeutic strategies for each potential category.

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ABBREVIATIONS

ACNS	American Clinical Neurophysiology Society
AIS	arterial ischemic stroke
ASM	antiseizure medicine
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
cVST	cerebral venous sinus thrombosis
DWI	diffusion-weighted imaging
EEG	electroencephalography
GBS	group B <i>Streptococcus</i>
HIE	hypoxic-ischemic encephalopathy
HSV	herpes simplex virus
ICH	intracranial hemorrhage
MCA	middle cerebral artery
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
NAS	neonatal abstinence syndrome

Objectives After reading this article, readers should be able to:

1. Identify clinical examination findings suggestive of encephalopathy in a term infant.
2. Recognize the most common causes of neonatal encephalopathy.
3. Understand the initial evaluation for neonatal encephalopathy.
4. Understand treatment options and outcomes for neonatal encephalopathy with different causes.

INTRODUCTION

Neonatal encephalopathy is a heterogeneous condition that results from a number of disorders that impair central nervous system (CNS) function within the first several days after birth (Table 1). It can be transient or indicative of permanent cerebral dysfunction. Maternal history, delivery and perinatal course, and physical examination can provide clues to the etiology of neonatal encephalopathy. Clinical signs can include poor feeding, respiratory insufficiency, and seizures. Physical examination findings of encephalopathy can involve level of consciousness, tone, reflexes, autonomic instability, and seizures (Table 2). All neonates with encephalopathy should be evaluated for infection, acute brain injury, and seizures (Table 3). This includes laboratory studies, brain imaging, and video electroencephalography (EEG). Evaluation should be expanded or tailored based on the clinical scenario. Intensive care practitioners should also use “neuroprotective measures” (Table 4) for all neonates with encephalopathy to minimize brain injury and optimize recovery.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

HIE is the most common cause of neonatal encephalopathy. Use of the term “HIE” to describe the encephalopathy presumes that it is the direct result of a perinatal hypoxic, ischemic, and/or asphyxial event. Because of differences in the definition of HIE and inclusion criteria for population studies of HIE, the incidence has been difficult to define. It is estimated to occur in approximately 1.5 per 1,000 term births (3)(4)(6) and accounts for 15% to 35% of all cases of neonatal encephalopathy in late preterm and term infants, depending on which clinical criteria are used to directly or indirectly infer a hypoxic-ischemic sentinel event. (7) Studies that retrospectively examined risk factors for HIE in late preterm and term neonates suggest that in addition to a clear sentinel event, other indirect intrapartum factors may

TABLE 1. **Differential Diagnosis for Neonatal Encephalopathy**

Infectious
Sepsis
Meningoencephalitis
Vascular/perfusion-related
Hypoxic-ischemic encephalopathy
Arterial ischemic stroke
Cerebral venous sinus thrombosis
Intracranial hemorrhage
Metabolic
Transient metabolic disturbances
Transient endocrinopathies
Inborn errors of metabolism
Toxicity/medication-related
Intrauterine drug exposure
Prenatal medication exposure
Intrapartum medication exposure
Postnatal medication administration
Epileptic
Acute symptomatic seizures
Neonatal-onset epilepsy/epileptic encephalopathy
Genetic/congenital
Systemic genetic syndromes
Inborn errors of metabolism
Congenital brain malformations

be associated with HIE, including abnormal fetal heart tracings, prolonged rupture of membranes, a tight nuchal cord, shoulder dystocia, thick meconium, or a failed vacuum delivery. (8)

TABLE 2. Examination Findings Suggestive of Encephalopathy in a Term Infant

Level of consciousness	Hyperalert or lethargic to obtunded
Muscle tone	Hypotonic
Posture	Distal flexion
Deep tendon reflexes	Increased
Suck	Weak or absent
Moro reflex	Incomplete or absent
Autonomic features	Tachycardia or bradycardia Desaturations or apneas
Seizures	Focal/multifocal

HIE is thought to represent a global hypoxic insult to the brain. (9) The injury proceeds through 3 phases, including the initial hypoxic-ischemic insult, followed by secondary effects, such as mitochondrial deficiency, oxidative stress, excitotoxicity, inflammation, and early stages of neuronal necrosis and apoptosis. (9)(10) The third phase encompasses long-term cell death, inflammation, cell turnover and repair, and gliosis. (9)

Magnetic resonance imaging (MRI) is the imaging modality of choice to evaluate the extent of hypoxic-ischemic injury (Fig 1), because it offers a more complete and high-resolution image compared with ultrasonography or computed tomography (CT). Typically HIE appears in 1 of 2 patterns: 1) symmetric bilateral parasagittal watershed infarcts involving cortical gray matter and subcortical white matter are thought to reflect prolonged partial hypoxic injury, and 2) involvement of the basal ganglia, thalami, brainstem, hippocampi, and Rolandic cortices is thought to reflect an acute profound global hypoxic injury to these highly metabolically active structures. Features of both patterns can be observed across the spectrum of HIE severity. (11)(12)(13)(14) Over time, brain MRI can evolve to show chronic changes in the areas of acute injury, which may include atrophy to the cortex and deep gray nuclei, ulegyria, or cystic encephalomalacia. (14) When performing brain MRI, it is crucial to consider the timing of image acquisition relative to the presumed injury. MRI performed before 2 days of age may only show subtle changes on conventional anatomic sequences (T1 and T2), and magnetic resonance spectroscopy and diffusion-weighted imaging (DWI) are needed to reveal evidence of injury. (12)(15)(16)

If imaging is performed after about 7 days (or after 10 days in infants who have received therapeutic hypothermia), DWI may “pseudonormalize,” and conventional sequences become more useful for interpretation. (12)(13)(15)(17) Many centers perform imaging between 3 and 5 days of age, after the infant has completed 72 hours of therapeutic hypothermia and while imaging changes are apparent on both conventional sequences and DWI. (12)(15)(16)

Currently, the only therapy with proven efficacy for HIE is therapeutic hypothermia. Multiple trials have demonstrated safety and efficacy of whole body and head cooling to improve outcomes for late preterm and term infants if initiated within the first 6 hours after birth. (18)(19) Cooling is hypothesized to reduce the detrimental consequences of secondary injury and inflammation. (18) Newer studies have examined adjuvant therapies, such as erythropoietin, with phase II studies showing promising results, (19) (20) though the results of larger multicenter trials are still pending. (21)

For more detail on the pathophysiology, clinical presentation, therapies, and outcomes for HIE, the authors recommend several review articles. (19)(22)(23)(24)(25)

Infectious

Infection should always be considered as a cause of neonatal encephalopathy. Risk factors for neonatal infection in term neonates include maternal infection at the time of delivery, prolonged rupture of membranes, and maternal group B *Streptococcus* (GBS) colonization. (26) Neonatal sepsis and histologic infiltration of the umbilical cord are independent risk factors for neonatal encephalopathy (odds ratio, 8.67 and 11.80, respectively). (27) Clinical signs of infection as the cause of encephalopathy include temperature instability (hypo or hyperthermia), hypotension, apneas/bradycardias, jaundice, and lethargy. (28)

Laboratory evaluation should include blood, urine, and cerebrospinal fluid (CSF) cultures. (29)(30) If disseminated herpes simplex virus (HSV) infection is suspected (either from maternal symptoms or suspicious skin lesions on the infant), skin culture specimens from multiple sites and a CSF specimen should be tested for HSV. (31) Chest radiography should be performed in infants with respiratory symptoms. Additional studies including a complete blood cell count, C-reactive protein, and procalcitonin can be helpful, but should not preclude diagnosis because these findings can be normal in neonates with sepsis. (32)

Clinicians should have a low threshold to treat early with empiric antibiotics and antivirals based on determination of early- or late-onset sepsis, and of the resistance pattern of the neonatal unit. (28) Antibiotics with CNS coverage and

TABLE 3. Recommended Diagnostic Evaluation for Neonatal Encephalopathy

<i>All infants with encephalopathy</i>	
Examination	Routine head circumference
Serum	Blood gas, lactate, comprehensive metabolic panel, complete blood count, newborn screen
Imaging	Head ultrasound, MRI brain without contrast, MRS
Other	EEG
<i>Infectious</i>	
Serum	Blood culture
Urine	Urinalysis and urine culture
Other	CSF studies and culture
<i>Vascular</i>	
Examination	Daily head circumference, particularly if hemorrhage
Serum	Coagulation studies ^a
Imaging	MRA, MRV
<i>Metabolic</i>	
Serum	Ammonia, pyruvate, plasma amino acids, acylcarnitine profile, carnitine level
Genetic	Karyotype, SNP array, mitochondrial panel, whole-exome sequencing
Urine	Urinalysis, urine organic acids
Imaging	MRS
<i>Toxicity/medication-related</i>	
Examination	Routine scoring for neonatal abstinence syndrome
Urine	Toxicology
Meconium	Toxicology
<i>Epileptic</i>	
Genetic	Targeted neonatal epilepsy gene panels
<i>Genetic/congenital</i>	
Examination	Daily head circumference, particularly if hydrocephalus
Genetic	Karyotype, SNP array, mitochondrial panel, whole-exome sequencing

CSF=cerebrospinal fluid; EEG=electroencephalography; MRA= magnetic resonance angiography; MRI=magnetic resonance imaging; MRS= magnetic resonance spectroscopy; MRV= magnetic resonance venography; SNP=single nucleotide polymorphism

^aNote that thrombophilia studies are thought to be of low yield in the acute stage.

acyclovir should be used for children with encephalopathy and suspected sepsis. Suspicion or confirmation of meningitis/encephalitis determines duration of treatment. (32) For infants with HSV meningitis/encephalitis, extended treatment with acyclovir can improve long-term developmental outcomes. (33)

Neonatal sepsis is estimated to cause one-third of all infant deaths annually and carries a significant risk of disability. (28)

Infants with meningitis/encephalitis have a high risk of sustaining white matter injury and neurodevelopmental sequelae. (28)

Vascular

Arterial Ischemic Stroke. Perinatal arterial ischemic stroke (AIS) is defined as an occlusive cerebral arterial event, typically thromboembolic, which occurs after 20 weeks'

TABLE 4. **Neuroprotective Measures for Neonates with Encephalopathy**

Temperature	Therapeutic hypothermia if indicated; otherwise maintain normothermia Treat fever
Ventilation	Maintain normocapnia and avoid hypocapnia
Oxygenation	Maintain normoxia
Glucose	Maintain euglycemia
Blood Pressure	Maintain normotension

Adapted from Glass et al. (97)

gestational age and before postnatal day 28. (34)(35)(36)(37) The precise term “arterial ischemic stroke” is purposefully chosen to distinguish arterial from venous vascular causes (discussed later in this article) and to distinguish the ischemic nature of the insult from hemorrhagic stroke (also discussed later). The prevalence is estimated at approximately 1 per 4,000 to 5,000 births, and the vast majority occur in late preterm and term infants. (34)(35)(38)(39)

Although the exact pathogenesis of perinatal AIS is unknown and is likely heterogeneous, several maternal and intrapartum risk factors have been associated with AIS. (35) These include a maternal history of infertility (requiring the use of ovarian stimulating medications), preeclampsia, chorioamnionitis, and prolonged rupture of membranes, (35)(40) which are linked to placental vasculopathy and a proinflammatory, prothrombotic state. A combination of prenatal risk factors further raises an infant’s risk of perinatal AIS. (35) Congenital heart disease is another predisposing risk factor for cardioembolic sources of AIS. (38)(41) Other less common risk factors that may increase the risk of AIS include congenital vascular malformations, trauma, and arterial catheterization or the requirement for extracorporeal membrane oxygenation. (38)(41) An association between prothrombotic disorders and AIS has not been confirmed in large prospective studies, calling into question the usefulness of routine thrombophilia testing in patients with AIS. (38)(42)

Over half of neonates with AIS will be acutely symptomatic (34) and present with generalized findings of neonatal encephalopathy, such as seizures, depressed level of consciousness, or abnormal tone. (36)(38)(43) Acute symptomatic seizures are the most common manifestation of perinatal

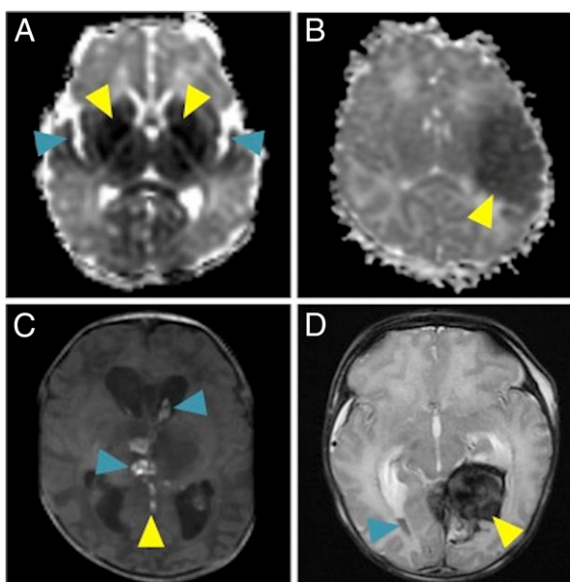


Figure 1. A. Apparent diffusion coefficient sequence from a 4-day-old term neonate demonstrating diffuse hypoxic-ischemic injury, with significant injury to the deep gray nuclei (yellow arrows), as well as the cortex (blue arrows). B. Apparent diffusion coefficient axial magnetic resonance imaging (MRI) scan of a 2-day-old term neonate with a left middle cerebral artery distribution of arterial ischemic stroke (yellow arrow). C. T1-weighted axial MRI scan of a 28-day-old neonate with extensive venous sinus thrombosis (yellow arrow corresponds to hyperintense clot in the vein of Galen and straight sinus) complicated by a right thalamic hemorrhage with intraventricular extension (blue arrows). D. T2-weighted axial MRI scan of a 1-day-old term neonate showing a largely extra-axial hemorrhage with a smaller intraparenchymal component within the left medial temporal lobe (yellow arrow), as well as intraventricular extension in the occipital horn of the right lateral ventricle (blue arrow). The hemorrhage was presumed to be secondary to cerebral venous sinus thrombosis.

AIS, occurring in 46% to 97% of neonates who present with AIS. (34)(38)(43)(44)(45) Focal motor seizures are a common clinical presentation of perinatal AIS, whereas focal motor asymmetry on examination is uncommon. (44) At most, focal motor deficits have been reported in 16% to 30% of infants with AIS, (38)(44) but other studies report closer to a 3% to 7% incidence. (34)(43) Thus, the absence of focal motor deficits should not reassure clinicians against AIS.

When AIS is not acutely symptomatic in the neonatal period, which happens in about 42% of patients, it is typically diagnosed later, when older infants or toddlers present with delayed developmental milestones, early handedness before 1 year of age, or evidence of monoplegic or hemiplegic cerebral palsy. (34)

Brain MRI is the imaging modality of choice for diagnosing AIS (Fig 1). In the acute phase, ischemic stroke is first evident as a diffusion-reduced lesion, followed by the age-dependent emergence of T1 and T2 signal changes in the affected territory. (14)(37) Long-term evidence of a remote perinatal insult is typically identified as an area of

encephalomalacia on brain MRI. (14) Imaging abnormalities are apparent within the vascular distribution of the affected vessel, which in the vast majority of perinatal stroke cases (74%), is the middle cerebral artery (MCA), with a predilection for the left MCA (53%) over the right (35%). (35)

Unlike in adult stroke, the interventions available for perinatal AIS are minimal. Typically, acute therapy is devoted to supportive care and neuroprotective measures (Table 4). (37) Because of a low incidence of recurrence, (46) there is little indication for acute or ongoing anticoagulation for perinatal AIS, unless there is a cardioembolic source. (47)(48) Long-term interventions are geared toward minimizing sequelae of perinatal AIS, including rehabilitation with physical and occupational therapy, use of orthotics, orthopedic surgical interventions, and pharmacologic treatment of epilepsy, pain, and spasticity. (49)(50) Early establishment of these services may help optimize outcomes. (49) An in-depth discussion of the long-term approach to therapy for perinatal AIS is discussed in detail elsewhere. (49)(50)

Cerebral Venous Sinus Thrombosis. Neonates have the highest lifetime incidence of cerebral venous sinus thrombosis (cVST), typically estimated between 0.3 and 2.6 per 100,000, though rates as high as 12 per 100,000 have also been reported. (51)(52)(53) Risk factors for cVST include gestational diabetes, gestational hypertension, premature rupture of membranes, chorioamnionitis, neonatal sepsis, meningoencephalitis, dehydration, prothrombotic disorders, and congenital heart disease, among others. (51)(54)(55)(56)(57)

Infants with cVST typically present with seizures, depressed level of consciousness, or diffuse jitteriness, and less commonly with focal deficits on examination. (51)(56)(57)

Brain MRI with magnetic resonance venography (MRV) is the imaging modality of choice for cVST (Fig 1). Ultrasonography with Doppler can also help with the diagnosis of cVST if MRI/MRV is not immediately available. (57) Imaging reveals disruption of venous blood flow at the area of thrombosis, which occurs more commonly in the superficial venous system than the deep venous system. (51)(55) Close to half of neonates with cVST have an associated parenchymal infarct, which is most often hemorrhagic. (51)(54)(56)(58) The parenchymal location of the hemorrhagic lesion is a relatively reliable indicator of the localization of the occluded vein or sinus. (57) Intraventricular hemorrhage in a term neonate should alert the clinician to the possibility of deep cVST. (59)

Supportive treatment of cVST includes intravenous hydration, particularly if dehydration is thought to be a provoking factor, as well as treatment of underlying infection, control of

seizures, and neurosurgical intervention for hemorrhage and/or hydrocephalus if warranted. (55) Screening for genetic evidence of thrombotic disorders can be performed, but functional studies are thought to be of highest yield when repeated outside the period of acute illness. (57) The use of anticoagulation for cVST is controversial. Consensus guidelines (57)(60) lean toward recommending anticoagulation with unfractionated or low-molecular-weight heparin in neonates with cVST, even in the presence of cerebral hemorrhage. This is because the complications of untreated cVST—infarct, hydrocephalus, and death—can be devastating. Some clinicians may hesitate to use anticoagulation because of concerns about provoking or exacerbating hemorrhage, but multiple case series appear to confirm that the risk of additional hemorrhagic complications is low. (53)(56) Reassuringly, the vast majority of thrombosed vessels will recanalize after several months regardless of anticoagulation therapy. (56)

Intracranial Hemorrhage. A final vascular cause of neonatal encephalopathy is intracranial hemorrhage (ICH). Hemorrhage can occur in multiple anatomic compartments, including epidural, subdural, subarachnoid, intraparenchymal, or intraventricular hemorrhage. Subdural hemorrhage is the most commonly detected compartmental hemorrhage, occurring in about 95% of infants with both asymptomatic and symptomatic ICH. (61)(62) Often, infants are found to have multifocal hemorrhage involving multiple anatomic compartments. (61)(62)(63)

The causes for ICH are diverse. Risk factors for ICH vary from prenatal complications, such as gestational hypertension, maternal drug use, or placental abruption, to intrapartum or postpartum factors, such as assisted delivery, birth trauma, perinatal asphyxia, or coagulopathy. (62)(64)(65) Primary vascular abnormalities, such as aneurysms, arteriovenous malformations, venous malformations, or cVST, are less common, but can also manifest with ICH. (51)(56)(65) Neonatal thrombocytopenia in particular is thought to be a specific risk factor for ICH. (63)(65)(66) Finally, genetic vascular disorders, such as mutations in *COL4A1/2*, which can present with perinatal ICH as part of a broader clinical spectrum, are increasingly identified. (67)(68)

Multiple case series have observed seizures or apnea as the presenting symptoms in the vast majority of infants with ICH. (62)(63)

Brain MRI is the ideal imaging modality for ICH (Fig 1), with MRV performed to evaluate for a cVST and magnetic resonance angiography performed to evaluate for an arterial anomaly. Ultrasonography and CT are less informative but can be useful if more rapid imaging is warranted. (65) If the cause of ICH is not clear from imaging, clinicians should consider genetic testing for heritable vascular disorders,

particularly if there is a strong family history or other syndromic features are present on examination.

Management of ICH in neonates begins with supportive care (Table 4): maintaining hemodynamic stability; treating seizures and infections; and correcting anemia, thrombocytopenia, or coagulopathy. (65) Obstructive hydrocephalus is a common complication of large intraventricular hemorrhage and infants' head circumference should be measured daily. Signs of increasing intracranial pressure, including increasing head circumference, bulging fontanel, or worsening encephalopathy, should alert the clinician to evaluate for hydrocephalus or recurrent or ongoing hemorrhage. (65) A few cases may require neurosurgical intervention, namely CSF diversion for severe obstructive hydrocephalus. (62)(63) Mortality from ICH is also variable, depending on the etiology, location, and severity of the hemorrhage, as well as comorbidities; however, outcome studies have shown that 75% to 100% of infants survive after ICH. (62)(63)

Metabolic

Transient Metabolic Disturbances. Neonatal encephalopathy can be a secondary manifestation of transient electrolyte imbalances or metabolic disturbances that are themselves the result of a diverse array of conditions, including systemic illness, specific organ malfunction, endocrine disorders, congenital disorders, or iatrogenic causes. A comprehensive list of all potential metabolic causes is beyond the scope of this review. However, we will include some specific examples to illustrate the appropriate evaluation for metabolic causes of neonatal encephalopathy.

Of the major electrolyte derangements, abnormal levels of sodium, calcium, and magnesium in particular can lead to altered mental status, seizures, and other neurologic sequelae. (69) Neonates have immature kidneys and mineralocorticoid resistance and are therefore susceptible to electrolyte imbalances, particularly hyponatremia. (70) Secondary causes of electrolyte abnormalities are also common, because hyperkalemia, hypernatremia, and hyper- and hypocalcemia occur frequently in neonatal sepsis. (71) Care should be taken with hydration and electrolyte repletion, because iatrogenesis is also a culprit of neonatal electrolyte disorders. (70)

Neonates are also particularly susceptible to encephalopathy from hypoglycemia. Common risk factors for hypoglycemia include perinatal stress, sepsis, large-for-gestation size, intrauterine growth restriction, maternal diabetes, and polycythemia, whereas less common causes include inborn errors of metabolism, congenital heart disease, congenital hyperinsulinism, and insulin-secreting tumors.

(72)(73)(74) Although most infants with transient hypoglycemia are neurologically asymptomatic, brain injury and long-term neurologic deficits can result from prolonged or recurrent hypoglycemia, particularly when serum levels are less than 30 to 40 mg/dL (1.6–2.2 mmol/L). (72)(73) Hypoglycemic brain injury predominantly affects the parieto-occipital lobes, (75) though there can be variable localization of brain injury. (73) To help prevent long-term visual, motor, or developmental delay from severe neonatal hypoglycemia, (73) all neonates with encephalopathy should undergo frequent glucose monitoring with rapid dextrose repletion as needed.

Profound hyperbilirubinemia can cause a spectrum of neurologic dysfunction, from mild reversible symptoms to acute bilirubin encephalopathy and kernicterus with irreversible brain injury if left untreated. (76)(77) Although widespread screening for and treatment of neonatal hyperbilirubinemia have made neurologic injury increasingly rare, acute bilirubin encephalopathy is still estimated to occur in 1.6 per 100,000 live births. (78) Screening tools, such as the bilirubin-induced neurologic dysfunction score or the kernicterus spectrum disorder toolkit, have been developed to assess the probability of neurologic injury from hyperbilirubinemia, incorporating neurologic examination findings, such as the patient's mental status, muscle tone, and motor dysfunction. (77)(79) Clinicians should keep in mind, however, that these neurologic signs are nonspecific for hyperbilirubinemia and may be seen with the many causes of neonatal encephalopathy discussed in this review. Typically, imaging findings of kernicterus involve symmetric injury of the globi pallidi but can also involve other deep nuclei of the brainstem and cerebellum. (80)

Finally, hyperammonemia and hepatic encephalopathy secondary to acute liver failure is a rare cause of neonatal encephalopathy. Acute liver failure itself can result from a diverse array of hepatic insults, but cerebral edema with encephalopathy is an important, if often late, associated condition. (81)(82) Care is aimed at providing sedation and ventilation to the infant and correcting metabolic derangements and coagulopathies while diagnosis and mitigation of the underlying hepatic condition is under way. (81)(82) Neurologic management also includes the use of hyperosmolar therapy for cerebral edema and the reduction of intracranial pressure. (81)(82) Often liver transplantation is the definitive therapy; however, mortality from acute liver failure can be high. (81)(82)

Inborn Errors of Metabolism. Inborn errors of metabolism result from mutations in 1 or more genes encoding enzymes responsible for the utilization of macronutrients,

small molecules, vitamins, or metals, or in genes that play a role in organelle function, such as those involved in mitochondrial, lysosomal, or peroxisomal disorders. Although individually rare, inborn errors of metabolism encompass hundreds to thousands of uniquely described disorders. (83) Many can present in the neonatal period, with most cases accompanied by neurologic symptoms. (83)(84) Encephalopathy in particular can be a prominent symptom, often because of disorders that result in the accumulation of toxic metabolites. (83)(85) We will highlight illustrative examples that may be encountered by the general practitioner, but interested readers are referred to several thorough reviews on inborn errors of metabolism. (83)(84)

Typically, a temporal pattern of latent encephalopathy in a previously healthy-appearing neonate should alert the general practitioner to consider inborn errors of metabolism, especially disorders that lead to toxic accumulation of metabolites as a result of increasing enteric intake of macronutrients, which overwhelm the defective catabolic pathway. (83)(84)(85) Likewise, neonates who become encephalopathic during highly stressful, catabolic states, such as infection or steroid use, or after recent dietary changes, should be screened for inborn errors of metabolism. (83)(84)

If no immediate cause is found, evaluation of the encephalopathic neonate should include screening laboratory tests for inborn errors of metabolism (Table 3), particularly if associated with suggestive examination findings, such as dysmorphic features, hepatomegaly, congenital abnormalities of other organ systems, or abnormal odor. A basic metabolic panel may reveal hypo- or hyperglycemia, as well as an anion gap, suggesting the presence of organic acids. (83) Liver function tests are requisite to screen for hepatic dysfunction, and an elevated ammonia level may suggest disorders of protein metabolism including urea cycle disorders. (84) A blood gas measurement can reveal metabolic acidosis, and an elevated lactate level might indicate ongoing anaerobic metabolism, unmasking a mitochondrial disorder or other disorder of energy failure. (83) Plasma amino acids and urine organic acids can be useful in screening for aminoacidopathies and organic acidurias, which are other categories of protein utilization disorders. (84) Abnormalities in the acylcarnitine profile and carnitine levels may suggest impaired fatty acid metabolism. (83) A urinalysis result that is positive for ketones may support a fatty acid disorder, ketone utilization disorder, or other disorders of energy failure. (83) The newborn screen is a powerful parallel tool to evaluate for many metabolic disorders, however results are often delayed by several weeks and the specific disorders included in testing vary by state. (83)

MRI may reveal characteristic patterns of brain involvement, such as the distinct constellation of findings observed in maple syrup urine disease or the distinguishing patterns of white matter involvement in various leukodystrophies. (86)(87) Imaging may also reveal the presence of cerebral edema, as seen with hyperammonemia. (85) Finally, magnetic resonance spectroscopy is often included because it allows for the specific evaluation of certain metabolites in affected brain regions. (86) In certain conditions, seizures may be observed on EEG, as with severe hyperammonemia, which is epileptogenic, (85)(88) or with some inborn errors of metabolism that are associated with early refractory epilepsy. (83)

If an inborn error of metabolism is suspected as a cause of encephalopathy, immediate steps should be taken to restore an anabolic state and reduce catabolic factors. Infants should receive copious intravenous hydration with dextrose-containing fluids and care should be taken not to provide overly hypotonic fluids, which risk exacerbating cerebral edema. (83) Protein-free nutrition should be administered while urea cycle disorders, aminoacidopathies, and organic acidurias are being considered. (83) Hemodialysis may be considered if severe hyperammonemia or other presumed small-molecule toxicity is present. (83) Based on diagnostic results, and in consultation with metabolic disease specialists, more targeted dietary regimens and cofactor supplementation can then be implemented.

Toxicity/Medication-Related

A common and reversible cause of neonatal encephalopathy that should always be on the differential diagnosis is exposure to prenatal medications that cross the placenta, as well as postnatally administered medications with sedating effects. Likewise, prenatal exposure to illicit substances should also be considered.

A number of maternal medications administered during the perinatal period may affect the neonate either transplacentally or via breastfeeding, resulting in encephalopathy marked by irritability, feeding difficulties, altered crying, jitteriness, convulsions, or other abnormal movements. (89)(90) Maternal antiseizure medications (ASMs), tricyclic antidepressants, lithium, or selective serotonin reuptake inhibitors have been associated with convulsions and a withdrawal syndrome in neonates. (89) A less clear link has been suggested with maternal use of antipsychotics or benzodiazepines. (89) Maternal levothyroxine has also been associated with neonatal encephalopathy, as well as concurrent thyroid endocrinopathy. (1)

Intrauterine exposure to illicit substances, specifically opiates, has become an increasingly common phenomenon.

(91) Both illicit opiate use, as well as maternal opiate replacement therapy, can be associated with neonatal abstinence syndrome (NAS), which can present with elements of neonatal encephalopathy. (90) NAS is a well-studied syndrome with commonly accepted protocols for both pharmacologic and nonpharmacologic therapies. (92) It is also worth recognizing that polysubstance use is common, and while other illicit substances are less likely to cause an immediate and obvious neonatal encephalopathy, associated multifactorial comorbidities (eg, alcohol use, unstable housing, inconsistent prenatal care, and concurrent mental health disorders) can affect a neonate's long-term development. (91)

Postnatally, sedatives, ASMs, and opiate replacement therapy for NAS can iatrogenically (often intentionally) suppress a neonate's mental status. Here, the benefits of treating the underlying pathology need to be weighed against the risks of prolonged sedation on a case-by-case basis. Generally, clinicians should strive to provide supportive care while aiming to minimize excessive exposure to these medications as clinically able.

For any neonate with encephalopathy, the clinician should take a careful maternal social history, specifically inquiring about maternal medical history, prescription medication use, and illicit substance use. Toxicology screening can be performed on both the mother and neonate. Medications used during labor and delivery, as well as the infant's current medication list, should be reviewed thoughtfully with the goal of reducing any prolonged or unnecessary exposure to sedating agents. Supportive care and treatment of NAS should be undertaken accordingly.

Seizures/Epilepsy

Acute Symptomatic Seizures. Seizures are a common sign of neonatal encephalopathy and the seizures and their treatment may also contribute to ongoing encephalopathy. Acute CNS injury is the most common cause of seizures in neonates.

EEG is essential for identifying and characterizing seizures in neonates (Fig 2). The American Clinical Neurophysiology Society (ACNS) 2011 guidelines recommend continuous EEG monitoring for 24 hours in high-risk neonates, or until

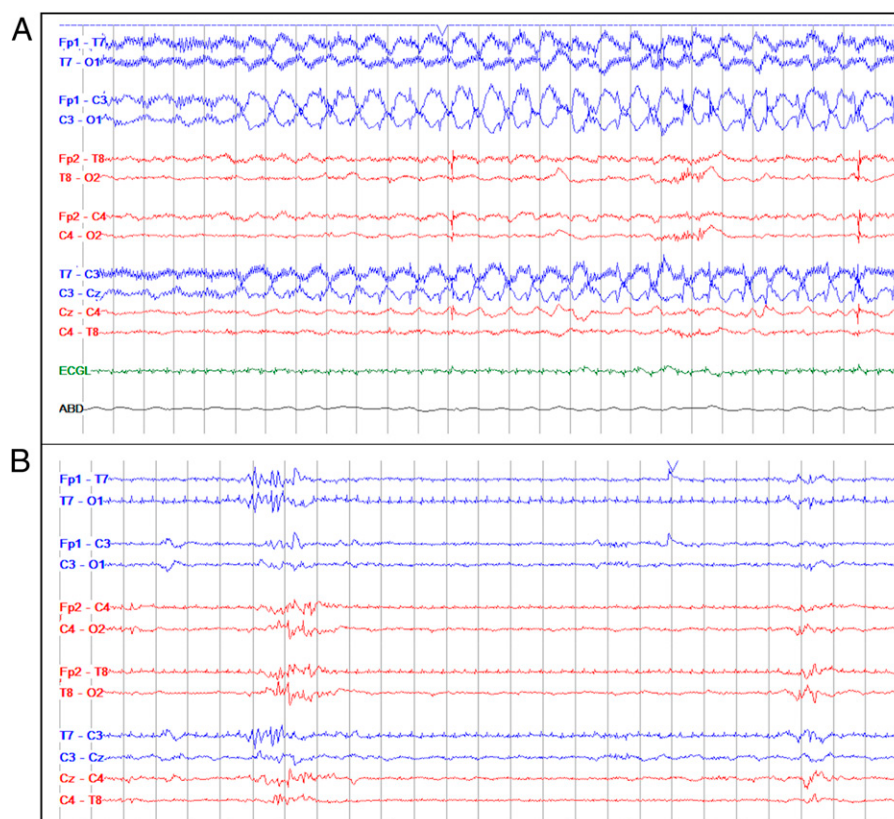


Figure 2. A. Example of left hemispheric seizure in a neonate. Clinically the infant had right leg clonic movements. B. Example of excessive discontinuity in a term neonate with encephalopathy. Electroencephogram viewed in neonatal bipolar montage, at a sensitivity of 7 μ V and timebase of 15 mm/sec.

paroxysmal events of interest have been captured, or at least 24 hours after the last electrographic seizure. (93) Neonatal seizures often do not have a clinical correlate, and clinical signs are easy to misinterpret, making them difficult to identify without EEG monitoring. Stereotyped events that should raise suspicion for seizures are focal tonic-clonic movements, fixed gaze deviation, myoclonus, bicycling movements of the legs, and autonomic paroxysms (unexplained apnea, cyanosis, cyclic tachycardia, or elevated blood pressures). (93) Seizures are more likely to be focal than generalized. (94)

Seizures in neonates should be treated with ASMs. Phenobarbital is the most commonly used ASM, followed by levetiracetam, fosphenytoin, and benzodiazepines. (95) A recent trial found that levetiracetam has far inferior efficacy compared with phenobarbital for seizures in neonates. (96) More than half of neonates will require 2 or more ASMs to control seizures. (95)(97)

Mortality is strongly associated with seizure burden, with mortality rate as high as 26% in neonates with status epilepticus. (95) EEG background can also provide valuable information about the degree of encephalopathy and prognosis. (98) When physical examination findings are obscured, such as when receiving sedative or paralytic medications, the degree of discontinuity seen on the EEG background can be a helpful objective marker of encephalopathy.

Neonatal-Onset Epilepsy. Although most seizures in neonates result from acute CNS injury, epilepsy syndromes can present in the neonatal period. About 13% of neonates with seizures have neonatal-onset epilepsy. (95) Seizures lasting longer than 72 hours should prompt evaluation for an underlying genetic or metabolic cause, which are important to recognize because the treatment may differ. For example, epileptic myoclonus can be associated with inborn errors of metabolism, such as vitamin B6 deficiency. (94) Family history of epilepsy may be a clue, as is seen in benign familial neonatal seizures caused by *KCNQ2* mutations.

Seizure semiology that includes tonic seizures, asymmetric posturing with shifting laterality, or spasms should raise suspicion for an epileptic encephalopathy. (99) In these cases, early recognition of electroclinical syndromes can allow precision medicine treatment. (99) A targeted gene panel should be used to evaluate for genetic causes of neonatal-onset epilepsy.

Congenital Brain Malformations

Congenital brain malformations are an uncommon cause of encephalopathy in neonates. A child may be diagnosed based on prenatal imaging (ultrasonography and MRI), and physical findings, such as micro- or macrocephaly, dysmorphisms, or neurocutaneous findings, can also be clues to an

underlying disorder (Fig 3). (100) Other examples include evaluating for midline defects that can suggest a disorder of holoprosencephaly spectrum. (101)

Evaluation should include genetic testing, starting with karyotype and chromosomal microarray, followed by targeted gene panel (if the clinical findings are suspicious for a particular syndrome) or whole-exome sequencing. (101) Treatment is supportive, but early identification can guide anticipatory management. For example, malformations of cortical development carry a higher risk of epilepsy. (102) ACNS guidelines recommend EEG monitoring for neonates with genetic syndromes including those of the CNS. (93)

Identifying congenital brain malformations can help with prognosis, guide future management, and alleviate parental distress. Infants with encephalopathy who have congenital malformations have a worse prognosis than infants with encephalopathy without malformations; they have double the risk of mortality at 2 years of age and are 3 times more likely to develop cerebral palsy. (103)

SUMMARY

- Neonatal encephalopathy describes a clinical constellation of neurologic symptoms that can include changes in mental status, from irritability to coma, hypotonia, abnormal movements, poor feeding, diminished primitive reflexes, and seizures.

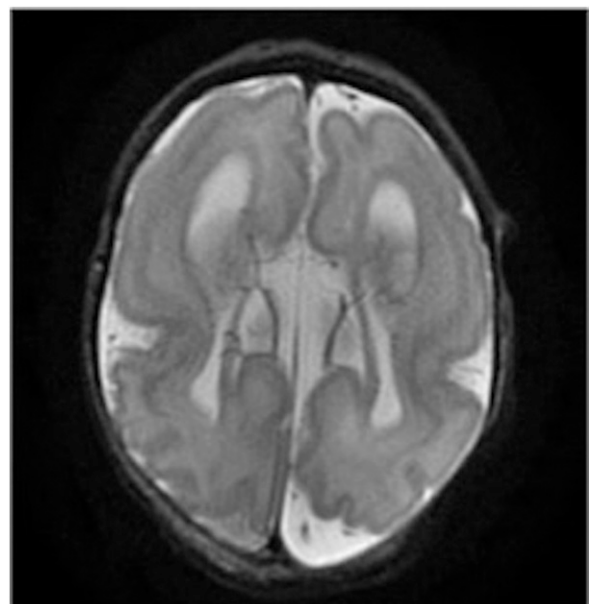


Figure 3. T2-weighted axial magnetic resonance imaging scan of a 1-day-old term infant with encephalopathy caused by lissencephaly (secondary to *TUBA1A* mutation).

- Neonatal encephalopathy occurs in 2 to 6 per 1,000 term infants. (1)(2)(5)(6)
- HIE is encephalopathy that is presumed to be secondary to an intrapartum asphyxia event. HIE occurs in approximately 1.5 per 1,000 infants. (3)(4)(6)
- For encephalopathy secondary to HIE only, hypothermia is the only therapeutic intervention with proven beneficial neurologic outcomes. (18)(19)
- Other causes of neonatal encephalopathy include vascular, metabolic, toxicity/medication-related, infectious, genetic/congenital, and epileptic conditions.
- Neonatal encephalopathy can be multifactorial, and there can be overlap among the different causes.
- All neonates with encephalopathy should ideally receive basic serum studies, a brain MRI, and an EEG with additional targeted studies based on diagnostic considerations (Table 3).

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the physical findings indicative of neonatal encephalopathy.
- Know the clinical features diagnosis and management of perinatal hypoxic-ischemic encephalopathy.
- Know the neuroimaging features of hypoxic-ischemic injury in term infants.
- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the causes, clinical features, laboratory evaluation, and acute management of metabolic encephalopathies in newborn infants.
- Understand the clinical features of neonatal seizures, and their prognosis.

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1. Neonatal encephalopathy affects 2 to 6 per 1,000 term births and results from a number of disorders that impair central nervous system (CNS) function within the first several days after birth. Hypoxic-ischemic encephalopathy (HIE) represents the most common cause of neonatal encephalopathy and the injury following a hypoxic-ischemic insult has been shown to progress in 3 phases. Which of the following injury mechanisms is characteristic of the third and final stage of injury in HIE?
 - A. Mitochondrial deficiency.
 - B. Oxidative stress.
 - C. Excitotoxicity.
 - D. Cell turnover and repair.
 - E. Hypoxic-ischemic insult.
2. Perinatal arterial ischemic stroke (AIS) is defined as an occlusive cerebral arterial event occurring after 20 weeks' gestational age and before postnatal day 28. Which of the following findings represents the most common clinical presentation of AIS?
 - A. Focal motor deficits.
 - B. Acute symptomatic seizures.
 - C. Alternating hypotonia and hypertonia.
 - D. Motor asymmetry.
 - E. Deep tendon reflexes asymmetry.
3. Cerebral venous sinus thrombosis (cVST) can present in a neonate with seizures, encephalopathy, or diffuse jitteriness. cVST most commonly occurs in the superior venous system and is best viewed using brain magnetic resonance imaging (MRI) with magnetic resonance venography. What proportion of neonates with cVST also develops an associated parenchymal infarct?
 - A. Approximately 1%.
 - B. Approximately 10%.
 - C. Approximately 20%.
 - D. Approximately 50%.
 - E. Approximately 80%.
4. Several disorders of an inborn error of metabolism (IEM) can present as neonatal encephalopathy. The onset of encephalopathy in a previously healthy neonate or the presence of dysmorphic features, hepatomegaly, congenital abnormalities of other organ systems, and abnormal odor on physical examination should alert clinicians to the possibility of an IEM. Brain MRI with magnetic resonance spectroscopy can be helpful in diagnosing an IEM in a neonate with encephalopathy. The presence of abnormal brain MRI findings in the internal capsules, corticospinal tracts, globi pallidi, cerebellar white matter, and dorsal brain stem is suggestive of which of the following that may be a clue to diagnosis?
 - A. Mitochondrial disorder.
 - B. Maple syrup urine disease.
 - C. Urea cycle defect.
 - D. Hyperammonemia.
 - E. Aminoacidopathy.

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5. Neonatal seizures often do not have a clinical correlate, and clinical signs are difficult to interpret without electroencephalographic monitoring. Most neonatal seizures result from acute central nervous system injury such as HIE; however, several epilepsy syndromes can present in the newborn period. The presence of tonic seizures, asymmetric posturing with shifting laterality, or spasms should raise suspicion for an epileptic encephalopathy. What proportion of neonates with seizures have neonatal-onset epilepsy?

- A. 5%.
- B. 13%.
- C. 25%.
- D. 35%
- E. 50%.

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