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Neonatal Hypoxia and Seizures

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Educational Gap

With 1 to 3 in 1,000 term neonates experiencing seizures, pediatricians need to know how to determine the seizure cause and manage appropriately, using brain imaging and treatments such as therapeutic hypothermia, xenon, and other pharmacologic therapies, in order to minimize long-term sequelae and leverage the infant brain's tremendous capacity for repair in the first 2 years after birth.

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

1. Understand the pathophysiology of neonatal seizures.
2. Know the many disorders associated with seizures in the newborn.
3. Be aware of the characteristics of different neonatal seizure syndromes.
4. Know how to evaluate a newborn who is having seizures.
5. Be aware of the treatments for neonatal seizures.
6. Understand the characteristics and management of hypoxic-ischemic encephalopathy.

Introduction

Seizures occur during the newborn period at an incidence of ~1 to 3 per 1,000 infants born at term. (1)(2)(3) Numerous systemic and neurologic conditions can manifest as seizures. Cerebral hypoxia-ischemia, defined as partial lack of oxygen resulting in reduction of blood flow to the brain, is the most frequent cause of seizures in the newborn period. It is important to determine the cause of neonatal seizures and institute the appropriate therapy to minimize the long-term sequelae of both the underlying condition and the seizure.

Pathophysiology of Seizures

Seizures are paroxysmal alterations in neurologic function caused by excessive synchronous depolarization of neurons within the central nervous system. Regardless of the underlying pathology manifesting as a seizure, all seizures are due to a shift in cell energy. This shift can result from failure of the adenosine triphosphate (ATP)–dependent sodium-potassium (Na^+-K^+) pump, an imbalance of inhibitory and excitatory neurotransmitters, and both excessive synaptic release and diminished reuptake of glutamate producing increased levels in the synapses.

The neonatal brain is more susceptible to seizures than the mature brain because of a predominance of excitatory neurotransmitters and immature inhibitory systems. During the first few weeks after birth, excitatory activity via N-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptors predominates in the hippocampus and neocortex. Not only are the inhibitory systems, such as the substantia nigra, relatively underdeveloped in the neonatal brain, but NMDA and AMPA levels in the perinatal brain actually exceed those in adult cortical neurons. (4)

Abbreviations

AED:	antiepileptic drug
AMPA:	α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid
ATP:	adenosine triphosphate
CSF:	cerebrospinal fluid
HIE:	hypoxic-ischemic encephalopathy
MOCO:	molybdenum cofactor
NMDA:	N-methyl-D-aspartic acid

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Furthermore, γ-aminobutyric acid, the primary inhibitory neurotransmitter in adults, is paradoxically excitatory in the neonate, who has larger intracellular concentrations of chloride in immature neurons, further increasing the susceptibility of the neonatal brain to seizure activity. (5)

Clinical Manifestations

Newborns rarely have well-organized, generalized tonic-clonic seizures because cortical organization is needed to propagate and sustain generalized seizures. Newborns have immature synaptic connections and insufficient myelination in the cortical efferent systems to propagate seizures. In comparison with other primates, however, human newborns have more advanced limbic development and connections to the diencephalon and brainstem, commonly resulting in seizures that manifest as oral-buccal-lingual movements (sucking, chewing), oculomotor phenomena, or apnea. (4)(6)

Classification of Seizures

Neonatal seizures can be classified into four categories: subtle, clonic, tonic, or myoclonic. Subtle seizures are more common in premature infants and manifest most often as ocular phenomena (tonic horizontal eye deviation with or without eye jerking, sustained eye opening with ocular fixation), oral-buccal-lingual movements (chewing or tongue thrusting), or "bicycling" or stepping movements of the lower extremities. Subtle seizures are not consistently associated with EEG changes.

Clonic seizures tend to manifest as focal, slow, rhythmic jerks of the face, unilateral upper or lower extremities, trunk, or neck, and the infant usually remains conscious. With focal seizures, there is often a corresponding underlying focal condition, such as a cerebral infarct.

Tonic seizures can be focal or generalized. Focal tonic seizures result in sustained posturing of a limb or asymmetrical posturing of the trunk or neck, whereas generalized tonic seizures manifest as tonic extension of both upper and lower extremities. Tonic flexion of the upper extremities with extension of lower extremities actually may represent posturing, a movement frequently associated with severe intraventricular hemorrhage, but not necessarily resulting from a seizure.

Myoclonic seizures usually involve the flexor muscle groups and can be focal, multifocal, or generalized. These movements have a faster jerk speed than clonic seizures and are not commonly associated with EEG manifestations. (6)

Seizures can manifest as apnea. Apnea secondary to seizures is more common in the term than the preterm infant. Most infants who have apnea secondary to a seizure also exhibit other subtle phenomena, such as eye opening, staring, and deviation or stereotypical mouth movements during the apneic episode, which can guide the clinician to the diagnosis. In the premature infant, most apnea is not related to seizures. Bradycardia is less likely to be associated with apnea from a seizure than with nonconvulsive apnea. (6)

Differential Diagnosis of Neonatal Seizures

Hypoxic injury is by far the most common cause of seizures in the term neonate, accounting for 40% to 60% of seizures in the newborn period. (7)(8) The next three most common causes are intracranial hemorrhage, intracranial infection, and congenital brain malformations. Combined, these four causes account for 80% of all neonatal seizures.

Hypoxic–Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is defined as brain injury caused by the combination of inadequate oxygen delivery and blood flow to the brain. (9) HIE occurs in 2.5 per 1,000 term births in developed countries, with an up-to-10 times greater incidence in developing countries. HIE can be a devastating entity, with 15% to 20% of affected neonates dying during the newborn period, leaving an additional 25% or more with permanent neurologic deficits. (6) According to the American College of Obstetrics and Gynecology and American Academy of Pediatrics, the following criteria must be present in order to diagnose HIE resulting from perinatal asphyxia (10)(11):

Metabolic acidosis with pH <7.0

- on an umbilical cord gas measurement (arterial or venous) *or*
- within 1 hour of birth on infant arterial blood gas measurement

Base deficit ≥12 mEq/L
Apgar score ≤5 at 10 minutes with continued need for resuscitation
Presence of multiple organ system dysfunction
Clinical evidence of encephalopathy (hypotonia, abnormal oculomotor or pupillary movements, weak or absent suck, apnea, hyperpnea, or clinical seizures). (9)

Determining whether perinatal HIE is attributable to antepartum, intrapartum, or early postnatal events may

be difficult. It is estimated that 20% of events occur in the antepartum period, but the majority are due to intrapartum events. (12)(13) Any event that compromises the blood or oxygen supply to the fetus contributes to hypoxia. These occurrences include maternal events (hemorrhage, amniotic fluid embolism, hemodynamic collapse); placental events (acute abruption); uterine events (rupture); umbilical cord events (tight nuchal cord, cord prolapse/avulsion); and intrapartum infection.

The pathophysiology of brain insult secondary to a hypoxic-ischemic event occurs in three stages over a 24- to 48-hour period: the immediate primary neuronal injury, a variable latent period, and finally late secondary neuronal injury. (14) Primary neuronal injury occurs with interruption of oxygen and glucose to the brain, resulting in decreased ATP and failure of the ATP-dependent Na^+-K^+ pump. Sodium enters the cell, followed by water, causing cell swelling, widespread depolarization, and cell death. Excessive stimulation by glutamate, an excitatory amino acid, results in an increase in intracellular calcium, activating a destructive cascade ultimately resulting in cell death.

If the neonate is resuscitated successfully, the period of primary neuronal injury is followed by reperfusion and a subsequent latent period, during which some neurons recover partially, only to die several hours later. The latent period lasts ∼6 hours and is followed by a period of secondary neuronal injury lasting 24 to 48 hours.

As with the period of primary neuronal injury, the period of secondary neuronal injury is mediated by damage to cerebral phosphate compounds, increased intracellular calcium, and elevated extracellular glutamate. The cerebral phosphate compounds (eg, phosphocreatine, ATP) and energy state begin to deteriorate at several hours of postnatal age. This deterioration continues for several days.

Elevated intracellular calcium causes neuronal injury by several mechanisms: activation of phospholipases, proteases, and nucleases; cytoskeletal disruption; and injury to the nucleus and cell membrane. When calcium enters the mitochondria and uncouples oxidative phosphorylation, glutamate is released. Not only are increasing amounts of glutamate released abnormally, but also the mechanisms for neurotransmitter uptake are disrupted because of hypoxia-induced failure of the Na^+-dependent glutamate transmitter.

The result is excess synaptic glutamate levels and activation of NMDA and AMPA receptors. These changes cause a further influx of Na^+ and calcium, followed by water and chloride, again resulting in cell swelling and lysis. Reactive oxygen and nitrogen species are generated as well, which contribute independently to neuronal injury. (9)(10)

The signs of HIE evolve over a period of days, highlighting the importance of careful serial neurologic examinations. Encephalopathy can manifest as a depressed level of consciousness during the first hours after an insult, perhaps accompanied by periodic breathing with apnea or bradycardia. Cranial nerve function, pupillary responses, and spontaneous eye movements are spared in less severe cases. Hypotonia develops with injury to the cortex. (15) Transient improvement in the level of alertness may occur during the first week, but this finding may not necessarily be accompanied by other signs of improved neurologic function.

Seizures occur in the majority of patients who experience moderate to severe HIE. These seizures occur typically in the first 24 hours, with 60% occurring within 12 hours of birth. Seizures may become severe and frequent from 12 to 24 hours after birth. Most seizures are subtle, although focal clonic or multifocal clonic seizures do occur. Focal clonic seizures usually are associated with focal cerebral injury. Approximately 30% of term infants afflicted with HIE and seizures have a focal cerebral infarction. Often, these infants exhibit relatively few other overt signs of encephalopathy. (6)

Prognostication may be aided by the use of a classification scheme, such as the Sarnat stages of encephalopathy. By identifying the stage of encephalopathy, the practitioner can better inform an infant's family regarding morbidity and mortality resulting from the hypoxic-ischemic event (Table 1). (16)

Treatment of HIE has centered around minimizing the damage that occurs during secondary neuronal injury. Therapeutic hypothermia is now the standard of care for infants who experience HIE and is recommended by the International Liaison Committee on Resuscitation. For newly born infants ≥36 weeks' gestation requiring resuscitation at birth and having evolving moderate to severe HIE, cooling therapy to a core temperature of 33.5 to 34.5°C, accomplished either via a head-cooling cap or whole body cooling, should start within 6 hours. Moderate hypothermia should last for 72 hours and then be followed by rewarming for 4 hours. This therapy should be provided in neonatal intensive care facilities with experience in cooling. (17)(18)

Moderate hypothermia results in decreased mortality and decreased severe disability in survivors. The effectiveness of this therapy is evident in its low number-needed-to-treat of 9. Nine infants who have encephalopathy need to be treated with hypothermia for 1 to experience benefit. These results are most striking in the infants who had moderate encephalopathy. Interestingly, infants who had HIE who did not undergo therapeutic hypothermia and

Table 1. **Sarnat Stages of Acute Encephalopathy**

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic/obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased/absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial/salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
EEG findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1- to 1 1/2-Hz spike-and-wave	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration	<24 h	2–14 days	Hours to weeks
Poor outcome (death or moderate/severe disability)	Low, similar to healthy comparisons	32%[a]	72%[a]

Adapted from Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol.* 1976;33:696–705, and Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med.* 2005;353:1574–1584.
[a]When treated with therapeutic hypothermia.

also experience elevated core body temperatures have worse outcomes, with the odds of death or disability increased fourfold for each 1°C increase for those in the highest quartile of core temperature (>38°C). (19) Even when cooling therapy is not available, it may be beneficial to withhold an exogenous heat source from the asphyxiated term infant (eg, avoid heating to temperatures >36.5°C).

Adverse effects of moderate hypothermia generally are minimal, the most common being thrombocytopenia (30%), hypoglycemia, hypotension, sinus bradycardia, prolonged QT interval, and subcutaneous fat necrosis. (20) Subcutaneous fat necrosis is an uncommon dermatologic disorder that manifests as firm, subcutaneous nodules that can occur either during or after therapeutic hypothermia. Although the nodules are benign, necrosis can trigger systemic, life-threatening hypercalcemia. (21)

Other adjunctive therapies are being studied that may augment the benefits of hypothermia or may offer a therapy in remote areas lacking ready access to controlled hypothermia. Xenon is an antagonist of the NMDA subtype of the glutamate receptor and has been shown to be neuroprotective when used in conjunction with hypothermia by reducing neuronal death in neonatal rats with HIE, even when xenon administration is delayed for several hours. Disadvantages of xenon include the high cost and the need for closed-circuit delivery via mechanical ventilation and gas-recycling systems. (22) Several phase II trials are currently underway in human neonates. Other pharmacologic therapies are being investigated, with varying neuroprotective effects, including erythropoietin, melatonin, and etanercept, a tumor necrosis factor-α inhibitor. (23)(24) These therapies are likely to be used in conjunction with therapeutic hypothermia.

Brain imaging can be helpful in confirming the diagnosis of HIE, quantifying the extent of damage, and assisting prognostication. MRI is the most accurate modality in newborns. The most common MRI findings in the first week are loss of differentiation of the cerebral cortical gray-white matter, increased signal in the basal ganglia and thalamus, and decreased signal in the posterior limb of the internal capsule.

There is controversy regarding the optimal timing of MRI, because signals are influenced by both the timing of the scan and the region being examined. It is clear that MRI on the first day likely underestimates the extent of injury. The optimal timing for diffusion-weighted MRI is at 2 to 3 days, but better predictions of future impairment based on extent of the thalamus and basal ganglia can be made from conventional MRI during the second week after birth.

Intracranial Hemorrhage

Intracranial hemorrhage accounts for ∼15% of seizures occurring in the neonatal period. Subarachnoid hemorrhages, occurring most frequently in term infants, usually are of no long-term clinical significance. In an otherwise well-appearing infant who has an incidental subarachnoid hemorrhage, seizures or apnea often will occur on the second postnatal day, and the infant will appear well during interictal periods. If seizures occur on the day of birth or if the infant is not well appearing between seizures, it is important to consider HIE as an underlying cause. The seizures will subside as the hemorrhage heals.

Seizures resulting from intraventricular hemorrhage occur primarily in preterm infants and in infants who have the most severe hemorrhages with accompanying parenchymal involvement. An isolated subependymal germinal matrix hemorrhage is associated with seizures uncommonly. Seizures may occur if extension of the hemorrhage occurs into the ventricles with corresponding ventricular dilation, or when there is extension into the brain parenchyma. These seizures usually manifest with generalized tonic activity but can appear as subtle seizure activity.

Subdural hemorrhages often are traumatic and result in a cerebral contusion leading to seizures in 50% of affected infants. The seizures usually are focal and appear in the first 48 hours after an insult.

Central Nervous System Malformations

Developmental defects of the brain account for 5% to 10% of seizures in the neonatal period. Usually there is a disorder of neuronal migration resulting in cerebral cortical dysgenesis. Neuronal migration, the movement of millions of nerve cells from their sites of origin in the ventricular and subventricular zones to their ultimate location in the brain, peaks during the third to fifth months of gestation. Disorders of migration usually cause clinical deficits soon after birth. The neuronal migration disorders most commonly presenting with seizures are schizencephaly, lissencephaly, pachygyria, and polymicrogyria. (6) Newborns who have a neuronal migration disorder severe enough to cause seizures in the neonatal period will almost certainly have subsequent epilepsy.

Infection

Intracranial infections account for 5% to 10% of neonatal seizures and must always be considered as a possible cause in any infant experiencing new-onset seizures. Bacterial meningitis is due most commonly to group B *Streptococcus* or *Escherichia coli*. Gram-negative organisms are particularly notable for causing brain abscesses and cysts. Infants hospitalized for other causes may be at risk for catheter-related or hospital-acquired sepsis or meningitis. Nonbacterial causes of neonatal seizures include infection with toxoplasmosis, herpes simplex virus, group-B coxsackie virus, rubella, and cytomegalovirus.

Seizures occur in 50% of cases of bacterial meningitis. One half of the seizures are subtle and are likely the result of inflammation of the arachnoid. Focal seizures occur in the other half of cases and are due to ischemic lesions. A significant number of septic infants also develop seizures. Therefore, it is recommended that any infant who has proven bacteremia or septicemia who develops seizures undergo an evaluation for meningitis, including a cerebrospinal fluid (CSF) analysis.

Metabolic Disturbances

Numerous metabolic disturbances can cause seizures in the neonate. These conditions include electrolyte disorders, as well as amino and organic acidopathies and mitochondrial disorders. Electrolyte disorders that can cause seizures include hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, and hypernatremia.

Hypoglycemia is a common cause of seizures in infants who are small for gestational age and in those born to diabetic mothers. Seizures due to hypoglycemia often are preceded by other neurologic signs, such as jitteriness and hypotonia. The duration of hypoglycemia is the most important factor in the subsequent development of neurologic signs. Prompt recognition and treatment of hypoglycemia is imperative to prevent permanent neurologic sequelae.

The most common area of brain injury seen on MRI in infants who sustained severe hypoglycemia is
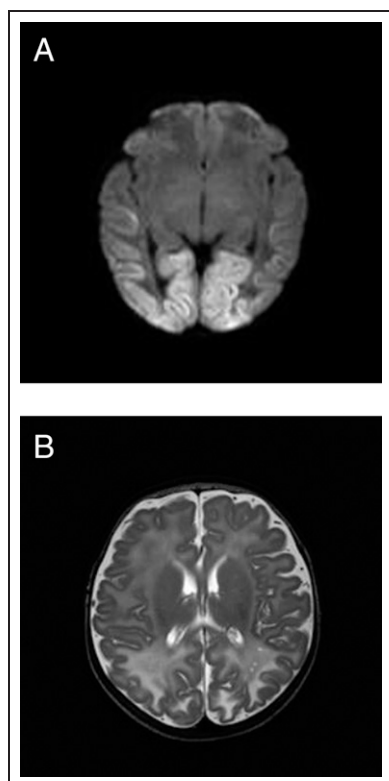
Figure. A. Brain MRI from a 4–day–old infant who experienced profound hypoglycemia. Note the restricted diffusion in the bilateral occipital and posterior parietal regions that can be seen with ischemia and severe hypoglycemia. **B.** Repeat MRI of same patient at age 6 weeks. Note the T2 hyperintensity in the bilateral occipital lobes consistent with gliosis from previous injury. There is also occipital lobe cystic encephalomalacia.

the occipital region (Fig). (25) This finding can differentiate brain injury caused by hypoglycemia from that caused by HIE, which often is global and affects the deep nuclei.

As with other electrolyte abnormalities associated with seizures, hypocalcemia is much more likely to coexist in an infant who has another cause of seizures (eg, HIE) rather than be the primary cause. There are two peak time periods for hypocalcemia to present in newborns. Infants who are premature, small for gestational age, or have diabetic mothers will present with seizures in the first 3 days after birth.

Hypocalcemia that appears later often is due to consumption of cow milk with high phosphorus content or to a syndromic (DiGeorge syndrome) or endocrine abnormality (hyperparathyroidism). Hypomagnesemia may accompany hypocalcemia or may exist primarily.

Both hyponatremia and hypernatremia can cause seizures. Hyponatremia in newborns commonly is iatrogenic, caused by administration of an excessive volume of hypotonic intravenous fluid or oral administration of free water. The syndrome of inappropriate antidiuretic hormone can occur with central nervous system disease (eg, meningitis, HIE, intraventricular hemorrhage, hydrocephalus) or with lung disease (eg, pneumonia). Rare causes of hyponatremia in a term infant are maternal water intoxication during labor (26) or a water birth that leads to excessive gulping of free water by the infant at time of birth. (27)

Although the metabolic disturbances due to inborn errors of metabolism are relatively rare, these disorders should be considered in infants who have seizures. Suspicion for an underlying inborn error of metabolism should be raised when there is severe and persistent hypoglycemia, metabolic acidosis or alkalosis, lack of a birth history suggesting perinatal oxygen deprivation, an elevated ammonia level, or congenital anomalies. Prompt diagnosis and treatment can, in some cases, prevent further damage to the infant's neurologic development (Table 2).

Nonketotic hyperglycinemia is a devastating progressive encephalopathy manifesting shortly after birth with lethargy, hypotonia, apnea leading to respiratory failure, and intractable seizures. This disorder is due to a defect in the glycine cleavage enzyme system. Laboratory findings are notable for a lack of metabolic acidosis, ketones, hyperammonemia, or signs of end-organ damage in an infant who appears to have been asphyxiated. The diagnosis is made by finding increased levels of CSF glycine. There is often a history of in utero and postnatal hiccups. Multiple therapies, including strychnine, tryptophan, and dextromethorphan, have been tried with limited success. Treatment with valproate paradoxically increases seizure activity by inhibiting glycine uptake in the mitochondria and increasing CSF glycine levels. (28)

Sulfite oxidase deficiency and molybdenum cofactor (MOCO) deficiency present soon after birth with feeding difficulties, vomiting, and seizures that are difficult to control. The clinical course progresses to spasticity, severe developmental delay, and microcephaly. Dislocated lenses and a seborrheic rash appear later in infancy. Sulfite oxidase deficiency can occur in isolation or as part of MOCO in 75% of cases. The diagnosis is made via mass spectrometry.

Simple screening analysis in an infant having seizures of unknown cause can include the use of a fresh urine sulfite strip test and testing for the presence of low plasma homocysteine or hypouricemia (in MOCO deficiency). There will be progressive destruction of neuronal structures and white matter on brain imaging.

> ## Table 2. Metabolic Disturbances Presenting With Seizures in the Neonatal Period
>
> **Organic aciduria/acidemia**
> - Methylmalonic acidemia, propionic acidemia, isovaleric acidemia
> - Severe acidosis, hyperammonemia, unusual odor, neutropenia, thrombocytopenia
>
> **Peroxisomal disorders**
> - Zellweger syndrome (hepatomegaly, renal and hepatic cysts)
> - Neonatal adrenoleukodystrophy
>
> **Urea cycle defects**
> - Ornithine–transcarbamylase deficiency (OTC) (X-linked recessive)
>
> **Nonketotic hyperglycinemia (NKH)**
> - Severe encephalopathy, hiccups; marked lack of acidosis, hypoglycemia, or hyperammonemia
>
> **Multiple carboxylase deficiency**
> - Holocarboxylase synthetase deficiency (hypotonia, vomiting, tachypnea, skin rash, metabolic ketoacidosis, hypoglycemia, moderate hyperammonemia); autosomal recessive
>
> **Glutaric aciduria, type II**
> - Severe hypotonia and nonketotic metabolic acidosis, hypoglycemia, hepatomegaly, polycystic enlarged kidneys, facial dysmorphism, rock–bottom feet, muscular defects of anterior abdominal wall, abnormal external genitalia, odor of sweaty feet, impaired cerebral neuronal migration; autosomal recessive
>
> **Molybdenum cofactor deficiency**
> - Presence of sulfites in urine, low plasma levels of homocysteine and uric acid
>
> **Pyridoxine dependency**
> - Dramatic improvement with administration of vitamin B_6
>
> **Folinic acid–responsive seizures**
> - Improvement with administration of folinic acid

Treatment involves a diet low in sulfur-containing amino acids, supplementation with sulfate, and administration of a MOCO precursor. However, these measures have not yet resulted in lasting clinical benefit. (6)(29)(30)

Multiple carboxylase deficiency has two basic types, one of which (holocarboxylase synthetase deficiency)

typically presents in the neonate. The underlying mechanism involves the metabolism of biotin, and the condition is inherited in an autosomal recessive pattern. This disorder presents clinically in the first days after birth with vomiting, tachypnea, hypotonia, seizures, and rash. Laboratory findings include ketoacidosis, moderate hyperammonemia, hypoglycemia, and elevation of several organic acids in the serum. Treatment is with high doses of biotin. Many state newborn screening programs include testing for this disorder.

Glutaric acidemia type II is due to a defect in the mitochondrial electron transport chain. This disorder can have a neonatal form that presents soon after birth with lethargy, tachypnea, vomiting, profound hypotonia, and seizures. These infants often are born prematurely and have congenital anomalies such as hepatomegaly, polycystic kidneys, rocker-bottom feet, anterior abdominal wall muscular defects, abnormal external genitalia, and an odor of sweaty feet. Neuronal migration defects affect the cerebral cortex. Despite a diet low in fat and protein, and supplementation with riboflavin and L-carnitine, the prognosis is poor.

The most common of the urea cycle defects, ornithine transcarbamylase deficiency is transmitted in an X-linked recessive fashion. Boys are affected most severely in the neonatal period and present often with feeding difficulties, lethargy, respiratory distress, impairment of consciousness, vomiting, seizures, and hyperammonemic encephalopathy. Plasma ammonia levels often are extremely elevated, and dialysis can be life saving during the acute presentation. Long-term treatment includes a low-protein diet, arginine supplementation, and sodium benzoate and phenylbutyrate administration to remove excess nitrogen.

Pyridoxine dependency is a rare autosomal recessive disorder of lysine degradation resulting in intractable seizures unresponsive to antiepileptic medication but responsive to treatment with vitamin B_6 (pyridoxine). The classic presentation occurs shortly after birth with refractory seizures. The infant may present with some symptoms of encephalopathy (apnea, lethargy, temperature instability), but there is no history of hypoxia. Burst suppression is a common EEG manifestation. (31) The diagnosis can be made clinically with resolution of seizures after administration of high-dose pyridoxine (100 mg IV) or by measuring increased α-aminoadipic semialdehyde in the urine. This deficiency also can be identified by a mutation in the ALDH7A1 (antiquitin) gene. Prompt diagnosis and treatment is imperative to reduce long-term cognitive impairment.

Folinic acid–responsive seizures present similarly to those of pyridoxine dependency but respond to treatment

with folinic acid. There is currently no test available, and diagnosis usually is made when seizures are controlled after empiric treatment with folinic acid. (32)

Neonatal Seizure Syndromes

Idiopathic syndromes of clinical seizures in newborns can be subdivided into the nonepileptic syndromes (benign neonatal sleep myoclonus, hyperexplexia) and the epileptic syndromes (benign familial neonatal seizures, benign idiopathic neonatal seizures, early myoclonic encephalopathy, early infantile epileptic encephalopathy). Infantile seizure syndromes, which present typically after the first month after birth, occasionally may manifest in the neonatal period.

Benign neonatal sleep myoclonus has its onset in the first week after birth and presents with clinical myoclonic seizures occurring only during non–rapid eye movement sleep. The infant manifests bilateral, synchronous, and repetitive movements of the upper or lower extremities (or both) that are provoked by gentle rocking of the crib in a head-to-toe direction and cease with the infant's arousal from sleep.

Hyperexplexia, or "startle disease," is a nonepileptic syndrome characterized by an exaggerated startle response with sustained tonic spasm to unexpected auditory, visual, or somatic stimuli. This reaction is caused by increased excitability of the reticular neurons in the brainstem. The mother may have noted sudden jerky movements of the fetus in utero, and hypertonia with an exaggerated startle response may be apparent from the first hours of postnatal age. The recurrent startle may result in increasing rigidity and jittery movements that become rhythmic and may mimic seizures. The tonic spasms can lead to apnea. Forced truncal flexion terminates the episodes. Clonazepam decreases the episodes, which ultimately disappear spontaneously by age 2 years. (33)

Benign familial neonatal seizures disorder is a rare autosomal dominant disorder that manifests with seizure onset on postnatal day 2 or 3. The infant can have 10 to 20 focal clonic or tonic seizures per day but appears well between seizures. The EEG shows brief flattening with apnea and tonic motor activity, followed by bilateral spikes and slow waves with clonic activity. The voltage-gated K$^+$ channel KCNQ2 encoded on chromosome 20 is implicated in 90% of affected cases. These seizures generally have a good response to antiepileptic medications, and affected newborns have normal neurologic development if their syndrome is self-limited, resolving in early infancy.

Another neonatal epileptic syndrome, termed benign idiopathic neonatal seizures, or fifth-day fits, is characterized by seizures peaking around the fifth postnatal day in otherwise apparently healthy term infants. This disorder manifests typically with multifocal clonic seizures accompanied by apnea. The seizures last <24 hours, but status epilepticus occurs during this time in a great majority of affected infants. Although the cause is not yet fully defined, both the possibility of acute zinc deficiency or mutations of KCNQ2, the K$^+$ channel most commonly affected in benign familial neonatal seizures, have been suggested. The outcome is favorable.

Early myoclonic encephalopathy is characterized by severe recurrent myoclonic and focal clonic seizures. The EEG shows a persistent suppression burst pattern enhanced during sleep. Multiple underlying causes have been implicated, primarily metabolic (eg, nonketotic hyperglycinemia). Seizure management is challenging, but the spells may respond to adrenocorticotropic hormone. The outcome is poor.

Early infantile epileptic encephalopathy, or Ohtahara syndrome, is a devastating disorder characterized clinically by severe recurrent "tonic spasms" and on EEG by burst suppression or markedly disorganized background rhythms. Over time, the EEG pattern evolves to hypsarrhythmia and West syndrome. The causes usually are structural (eg, neuronal migrational disorders). There have been reports of infants who have early infantile epileptic encephalopathy having CSF monoamine findings similar to aromatic acid decarboxylase deficiency who respond to treatment with pyridoxal 5-phosphate. As in early myoclonic encephalopathy, the seizures in this syndrome are difficult to control, but may respond favorably to adrenocorticotropic hormone; ultimately, these patients have a very poor outcome. (6)

Other Causes of Seizures
Drug Withdrawal

The neonate who was exposed passively to certain drugs in utero is at risk for the neonatal abstinence syndrome, a syndrome that can include seizures infrequently. Other signs and symptoms of neonatal abstinence depend on the specific maternal substance ingested, but include hyperirritability, hyperalertness, increased rooting and uncoordinated sucking, emesis, loose stools, yawning, and sneezing.

The drugs most commonly implicated are opioids (heroin, methadone, propoxyphene, codeine, oxycodone, hydrocodone, etc). Benzodiazepines, barbiturates, tricyclic antidepressants, cocaine, alcohol, pentazocine, and tripelennamine (the combination of the latter two is referred to as "Ts and Blues"), and the antidepressant class of selective serotonin reuptake inhibitors also may be associated with neonatal seizures or encephalopathy. (34)

Depending on the particular drug exposure and the extent to which the fetus was exposed (the maternal length of usage, amount of usage, and last usage before delivery), symptoms of abstinence and seizure can occur in the first 1 to 5 days after birth. Most of these passive exposures result in nonspecific withdrawal symptoms, but opioid withdrawal presents with a pathognomonic neonatal abstinence syndrome that usually is present when seizures occur. The seizures usually subside with appropriate treatment of the abstinence syndrome. Many drug withdrawal syndromes involve jitteriness that may be mistaken for seizures. Seizures resulting from use of tripelennamine may be a toxic effect of the drug because seizures are an adverse effect of this drug in adults.

Most abstinence syndromes develop within the first 24 to 48 hours after birth, although onset may be later if the mother used a long-acting drug (eg, methadone). Treatment of neonatal abstinence syndrome includes supportive measures, as well as appropriate drug therapy with tincture of opium, methadone, or morphine for opioid-exposed infants, in addition to phenobarbital or diazepam for seizures.

Local Anesthetic Infiltration

Local anesthetic infiltration is a rare cause of seizures immediately after birth. The typical scenario is an infant who develops tonic seizures in the first 6 hours after a birth in which a local anesthetic, typically for a paracervical or pudendal block, was inadvertently injected into the infant scalp. The newborn's pupils will be dilated and fixed to light, and a doll's eyes reflex may be present. The diagnosis can be made by history, measurement of anesthetic in the blood or CSF, and telltale marks on the scalp.

Electroencephalography

An important tool in the evaluation of infants who have seizures is the surface EEG. Clinical recognition of neonatal seizures is challenging because not only may neonates display behaviors concerning for seizures without an electrographic correlate, but also there may be seizure activity on EEG not clinically recognizable as a seizure. In neonates who have seizures and are monitored with continuous EEG, up to 79% of electrographic seizures are not accompanied by clinical seizure activity, and 47% of infants who have HIE and are undergoing head cooling experience electrographic seizures exclusively. (35)(36)

Despite these issues, a 1- to 2-hour EEG can confirm the clinical diagnosis of seizures, diagnose subclinical seizures, and show the level of background interictal involvement. Video-EEG for 12 to 24 hours often is useful to correlate specific physical manifestations with electrical activity. Because of immature myelination in neonates, abnormal signals from seizure activity in deeper areas of the brain may not be fully propagated to the surface for capture by the EEG.

Amplitude-integrated EEG can be a useful bedside tool for cerebral function monitoring in infants who have HIE. Its utility in the nonencephalopathic infant who has seizures is limited. This technique records a single-channel EEG that modifies the wave recording for bedside interpretation. The interpretation of the EEG is based on pattern recognition, and the study is useful for correlating the early findings of HIE with subsequent neurodevelopmental outcomes of term infants, especially those managed with normothermia. This type of EEG is not helpful in detecting subclinical seizures. (37)

Treatment

The conventional first-line treatment for neonatal seizures is phenobarbital administered intravenously (Table 3). Phenobarbital alone completely controls seizures in a little over 40% of cases. When combined with fosphenytoin, historically the second-line choice, 60% of cases are completely controlled. (38) Disadvantages of phenobarbital include sedation, which can impair clinical neurologic assessments. Like fosphenytoin, blood levels

Table 3. **Antiepileptic Drug Dosing**

	Loading Dose	Maintenance Dose	Mode of Administration
Phenobarbital	20 mg/kg. Refractory seizures: Additional 5 mg/kg doses up to a total of 40 mg/kg	3–4 mg/kg every 24 h IV, IM, PO, PR	IV, IM, PO, PR
Fosphenytoin	15–20 mg/kg	4–8 mg/kg every 24 h	IV, IM
Levetiracetam	10 mg/kg	Up to 30 mg/kg/dose every 12 h	IV or PO
Lorazepam	0.05–0.1 mg/kg		IV

IM=intramuscularly; IV=intravenously; PO=orally; PR=rectally.

need to be monitored. Phenobarbital induces neuronal apoptosis in many areas of the brain in rats, leading to concern for use in neonates, especially those who have HIE in whom there is already damage and death of neurons. Levetiracetam is well tolerated and, unlike phenobarbital and fosphenytoin, is not metabolized by the cytochrome P450 system, which can be altered in the face of systemic hypoxic injury. Levetiracetam's exact mechanism of action is yet to be elucidated but may involve prevention of hypersynchronization of epileptiform bursts and propagation of seizure activity. Lorazepam, a benzodiazepine, can be effective in infants who have seizures refractory to other antiepileptic medications. (39)

Duration of treatment with antiepileptic drugs (AEDs) depends upon the neurologic examination, frequency of seizures, EEG findings, and underlying etiology for seizures. On one extreme, infants who have cortical dysgenesis experiencing seizures in the neonatal period will almost assuredly have persistent seizure activity and require long-term AEDs. A neurologic examination with abnormal results is also associated with increased risk of persistent seizures. In general, consideration for trial of discontinuation of AEDs is made when infants are seizure free and have a neurologic examination with normal findings. If the results of the neurologic examination are abnormal, but the infant is clinically free of seizures and has a reassuring EEG, a trial off AEDs is appropriate.

Prognosis

The short- and long-term prognosis of neonates who develop seizures is highly variable and depends upon the

Table 4. Neonatal Seizure Prognosis, by Etiology

Neurological Disease	Abnormal Neurodevelopment, %
Bacterial meningitis	50
Hypoxic–ischemic encephalopathy	50
Hypocalcemia	
• Early-onset	50
• Late-onset	0
Hypoglycemia (profound/ prolonged)[a]	50
Intraventricular hemorrhage with parenchymal damage	90
Congenital brain malformation	100
Primary subarachnoid hemorrhage	10

[a]Whole-blood glucose <40 mg/dL for >4 hours.

cause for seizures (Table 4). An increased level of seizure complexity, persistent abnormal electrical activity, and need for multiple medications to control the seizures are all associated with worse developmental outcomes. Multiple repetitive seizures cause damage to developing cortical circuitry (40) and when superimposed on an already abnormal brain structure (such as with cortical dysgenesis), can have a devastating result. However, because there is so much brain plasticity in the first 2 years after birth, the infant brain has tremendous potential for repair, growth, and compensation after injury. It is important that a neurologist and a developmental pediatrician follow infants who have seizures with the goals of controlling seizures, minimizing medication adverse effects, and implementing early treatment of developmental disorders.

Summary

- Based on observational and animal studies, human newborns are more susceptible to seizures than older children. (5)(6)
- Based on observational studies and expert opinion, compared with older children, newborn infants are more likely to manifest seizures with oral–buccal–lingual movements, oculomotor phenomena, or apnea. (4)(6)
- Based on strong research evidence, the degree of severity of hypoxic–ischemic encephalopathy strongly influences the neurodevelopmental outcome of affected infants. (16)
- Based on strong research evidence, newborns who have hypoxic–ischemic encephalopathy should be treated with moderate hypothermia (head– or whole-body cooling). (17)(18)
- Based on some research evidence and consensus, newborns who have hypoxic–ischemic encephalopathy or clinical concern for seizures should undergo a bedside EEG. (35)(36)(37)
- Based on consensus, discontinuation of antiepileptic medications can be considered in infants without congenital brain malformations who are subsequently free of seizures (clinically and electrographically). (6)

Different types of neonatal seizures can be viewed as part of a recent article in NeoReviews. *All of these seizure types can result from hypoxia. To view these seizures, visit* neoreviews.aappublications.org/content/13/4/e213/suppl/DC1.

To view the references for this article, visit the September issue at http://pedsinreview.aappublications.org and click on "Neonatal Hypoxia and Seizures."

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit*[TM]. To successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*[TM], learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. A neonate experiences a moderate intrapartum hypoxic–ischemic event. The first seizure occurs 20 hours after birth. In such circumstances, seizures primarily reflect

   A. Destruction of inhibitory receptors.
   B. Inadequate intrasynaptic glutamate accumulation.
   C. Increased permeability of the cell membrane to sodium.
   D. Myelin destruction.
   E. Reduced permeability of the cell membrane to potassium.

2. A neonate experiences a moderate intrapartum hypoxic–ischemic event. Among the following therapeutic options, the choice that offers the best chance of minimizing secondary neuronal injury is

   A. Erythropoietin.
   B. Hypothermia.
   C. Melatonin.
   D. Phenobarbital.
   E. Xenon.

3. A 30-hour-old appropriate-for-gestational-age term neonate experiences recurrent brief apnea associated with wide opening of the eyes. In between the spells, the infant appears normal. Gestation was unremarkable. Maternal screening for infectious disease was negative. Rupture of membranes occurred 1 hour before delivery. The fluid was clear. Delivery was vaginal, vertex with Apgar scores of 7 at 1 minute and 9 at 5 minutes. The physical examination is unrevealing. Blood glucose is 75 mg/dL. The most likely explanation for the spells is

   A. A disorder of neuronal migration.
   B. Bacterial meningitis.
   C. Hypoxic–ischemic encephalopathy.
   D. Nonketotic hyperglycinemia.
   E. Subarachnoid hemorrhage.

4. You are seeing a 10-day-old boy whose mother is concerned about the simultaneous jerks of the upper and lower extremities that occur in her son during sleep. She first noted this when he was age 5 days. He was delivered vaginally at term with normal weight for age. His Apgar scores were 8 at 1 minute and 9 at 5 minutes. He left the hospital with his mother at age 2 days. He has been breastfeeding well and makes no unusual movements other than hiccups when awake. You suspect

   A. Benign familial neonatal seizures.
   B. Benign idiopathic neonatal seizures (fifth-day fits).
   C. Benign neonatal sleep myoclonus.
   D. Hyperexplexia (startle disease).
   E. Myoclonic encephalopathy.

5. A 1-day-old boy with suspected hypoxic–ischemic encephalopathy has two episodes of tonic horizontal eye deviation associated with rapid chewing movements. You suspect subtle seizures and decide to treat them. Which of the following anticonvulsants has been used in these circumstances, is well tolerated, and is not metabolized by the cytochrome P450 system?

   A. Ethosuximide.
   B. Fosphenytoin.
   C. Levetiracetam.
   D. Phenobarbital.
   E. Valproic acid.

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