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Educational Gaps

1. Physiological differences contribute to different appearances and drug responses in neonates as compared with older children.
2. Nonepileptic behaviors can be mistaken for neonatal seizures.

Abstract

Neonatal seizures are a common problem encountered or suspected by those caring for neonates. The estimated incidence of newborns affected is between 0.1% to 0.5%. Because several causes of seizures in newborns require rapid recognition and treatment to prevent further injury, early recognition is important. Seizures in newborns frequently have more subtle clinical manifestations than in older children. Electroencephalographic seizures without clinical signs present additional diagnostic and therapeutic challenges. This article reviews the various seizure types, etiologies, diagnostic modalities, and treatment options for neonates with seizures and seizure-like episodes.

Objectives

After completing this article, readers should be able to:

1. Be familiar with the different categories of neonatal seizures.
2. Know the common causes of neonatal seizures and recognize them as risk factors for seizure occurrence.
3. Understand the contribution of various electroencephalographic techniques to identification of neonatal seizures.

Introduction

Neonatal seizures are a common problem encountered by doctors and nurses caring for sick newborns. To recognize the often subtle clinical manifestations and treat the seizures and their underlying causes promptly, it is important to recognize the risk factors and potential causes of seizures in infants.

Epidemiology

Neonatal seizures are a relatively common occurrence. (1)(2) They are estimated to occur in ~0.1% to 0.5% of newborns. In underdeveloped countries, the estimates are even higher. Seizures are more common in the first week of life than at any other time. (3) Several factors account for this high incidence: the neonatal brain is more seizure-prone because of maturational factors, late gestational and birth-related injuries can provoke seizures, and congenital malformations, genetic disorders, and acute metabolic derangements are often manifest in the neonate. (4)(5)(6)(7)

Abbreviations

EEG: electroencephalographic
EIEE: early infantile epileptic encephalopathy
EME: early myoclonic encephalopathy
GABA: γ-aminobutyric acid

Pathophysiology

Seizures are caused by excessive, hypersynchronous neuronal activity, typically thought of as excessive excitatory or deficient inhibitory neuronal function. The newborn brain is more prone to deficient inhibition because γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in

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the more mature brain, has a net excitatory effect in infants. (8) The GABA receptor modulates chloride and potassium flux. Typically, there is a net influx of chloride which results in a decreased cellular membrane resting potential, countering the excitatory effect of depolarizing stimuli that initially cause an influx of positive sodium and calcium ions into the neuron via predominantly glutamate-modulated stimuli. In the immature brain, there is a relatively higher concentration of chloride in the neuron, so the overall inhibitory effect of GABA is muted and sometimes has a net excitatory effect, (9) which may explain the often incomplete response of neonatal seizures to commonly used seizure medications that act via GABAergic mechanisms (ie, phenobarbital and benzodiazepines). Phenobarbital acts by way of a more prolonged opening of the chloride channel, whereas benzodiazepines act via more frequent opening of the chloride channel.

Generally seizures are regarded as arising in the cerebral cortex. Stereotyped, paroxysmal seizure-like behavior that arises from subcortical structures such as the brainstem are characterized as "brainstem-release phenomena" or primitive reflexes "released" owing to a depressed cortex providing diminished inhibition on "downstream" neuronal structures. (10)

The immature GABAergic function matures in a caudal-to-rostral fashion. For this reason, GABAergic drugs can inhibit the motor "throughput" at a brainstem level, suppressing the motor manifestations of seizures while the cortex, with a persistent net excitatory GABA effect, continues to seize. (11) (See discussion of clinical and electroencephalographic [EEG] manifestation of seizures in the following sections.)

Clinical Manifestation

Neonatal seizures are typically more subtle than seizures in more mature children. At the time of birth, the brain does not have the capacity to manifest generalized tonic clonic seizures. There is incomplete myelination and less capacity for seizures to secondarily generalize from a single focus or for seizures from multiple foci to coalesce into a generalized seizure. (12) Neonatal seizures are most commonly classified within one of five basic categories: focal (or multifocal) clonic, focal tonic, generalized tonic, myoclonic, and subtle. (10)

Focal clonic seizures are the most easily recognized as "epileptic." They manifest as slow rhythmic jerking of an extremity or rhythmic twitching of the face. The rate is usually between 0.5 and 2.0 jerks per second. There is good correlation between the clinical seizure and the rate of the rhythmic epileptiform discharges on the EEG result (Fig 1). When clonic seizures in neonates look generalized, careful observation and analysis of the coincident EEG findings will show that there are independent bilateral seizures occurring with differing rates and different evolution (Fig 2). The main nonepileptic phenomena that may be mistaken for clonic seizures are jittery movements, limb clonus, and benign sleep myoclonus (Supplemental Video 1). (13)

Jittery movements often appear in infants who are recovering from an acute perinatal hypoxic insult or in those who are withdrawing from sedative and opiate medications (including maternal drug exposure). Jittery movements are usually very rapid, short-duration tremulous movements that are typically not isolated in one extremity from episode to episode. They occur when the infant is aroused and subside with sleep or sedation. During an episode they often abate when a limb is repositioned, unlike focal clonic seizures that persist despite limb repositioning.

Limb clonus typically is seen in infants who have emerging hyperreflexia after a previous brain insult such as hypoxia. The jerking of clonus usually is restricted to one joint (commonly the ankle), and it is rapid and of short duration. Repositioning the limb by reducing the stretch on the affected tendon (eg, plantar flexing the foot and knee) often causes the jerking to stop (Supplemental Video 2).

Benign sleep myoclonus usually involves one to five rapid jerks of a limb over a few seconds. The jerks involve the whole limb, the trunk, or the face. The quick jerks involve one limb, then another in a seemingly random fashion. Arousing the infant causes the jerks to remit.

Focal tonic seizures appear as slowly evolving stiffening and posturing of a limb. The movements from seizure to seizure are stereotyped. They cannot be interrupted consistently by repositioning, but of course may stop coincidentally with arousal or stimulation. Other clues as to the epileptic nature of the spells can include tonic eye deviation and head turning. As with focal clonic seizures, there is usually good correlation with an epileptiform rhythmic discharge on the EEG result (Supplemental Video 3).

Generalized tonic seizures are whole-body stiffening with limb extension or flexion and trunk stiffening. Tonic seizures usually occur in infants with a history of significant brain injury. The EEG reading may not reveal an ictal rhythmic discharge, suggesting that these events are not originating in the cerebral cortex and are more likely a brainstem-release phenomenon.

Myoclonic seizures are quick, single jerks of a limb or limbs and trunk. When repetitive, they are not rhythmic like clonic seizures. Myoclonic seizures may occur in the

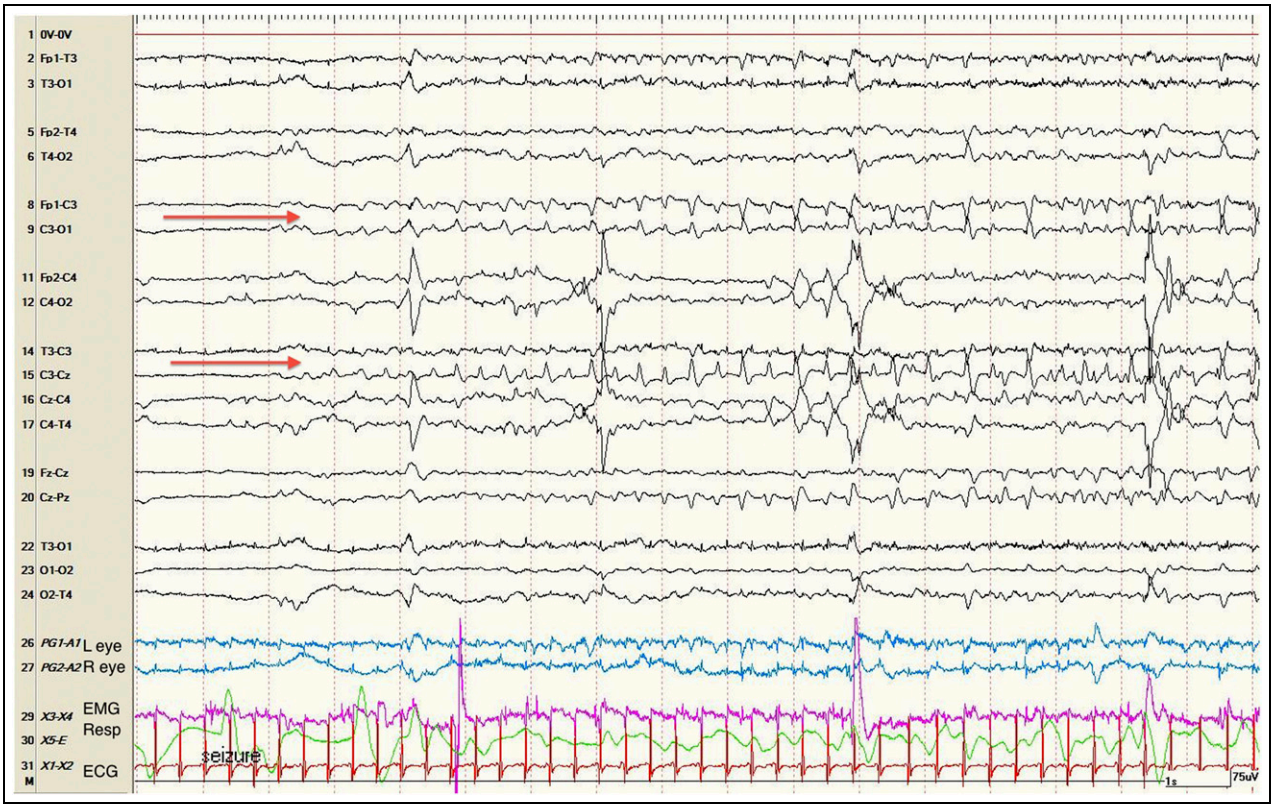

Figure 1. Evolving rhythmic ictal discharge maximum in EEG lead C3 (arrows). This EEG sample of a 3-day-old term infant with sepsis, hypocalcemia, and hypomagnesemia includes channels showing eye movement, chin electromyogram (EMG), respiration, and electrocardiogram (ECG).

setting of a recognized brain insult, but they also may be a first sign of an underlying metabolic or genetic condition. They are more persistent than benign sleep myoclonus and typically occur in wakefulness, not only in sleep. Jittery movements are usually more sustained for several seconds, whereas myoclonic seizures occur singly. There is often no coincident EEG ictal correlate (Fig 3, Supplemental Video 4).

Subtle seizures are the hardest seizures to differentiate from normal behavior and nonepileptic pathological behaviors. Subtle seizures are sometimes divided into subtle motor seizures and subtle autonomic seizures. Motor behaviors may be stereotyped spells of eye deviation and nystagmus, abnormal chewing movements, rhythmic tongue thrusting, swimming movements of the arms, or bicycling movements of the legs. Autonomic signs include tachycardia (more than bradycardia), apnea, and changes in blood pressure (typically sudden increases). Subtle seizures usually occur in infants with recognized encephalopathic conditions. The EEG reading sometimes shows an ictal correlate and sometimes does not.

Etiology

When infants present with seizures, the underlying cause must be investigated carefully. The first step is to look for correctable metabolic derangements that, if untreated, may lead to additional brain injury. Hypoglycemia in particular must be recognized and treated quickly to avoid further brain injury. Although infants born to mothers with diabetes are recognized easily as being at risk for hypoglycemia, other etiologies may be less readily suspected, such as hyperinsulinism. Other metabolic derangements that should be sought at the outset of seizure evaluation and treatment include hypocalcemia, hypomagnesemia, and hyponatremia.

The most common cause of neonatal seizures is perinatal asphyxia and other hypoxic conditions such as those caused by cardiac disorders. (14) In this setting, seizures usually manifest themselves in the first hours to the first day. (15) Depending on the degree of encephalopathy and the severity of the insult, the seizures may range from focal clonic seizures to subtle seizures.

Intracranial hemorrhage is another common cause of neonatal seizures. Even an apparently atraumatic delivery

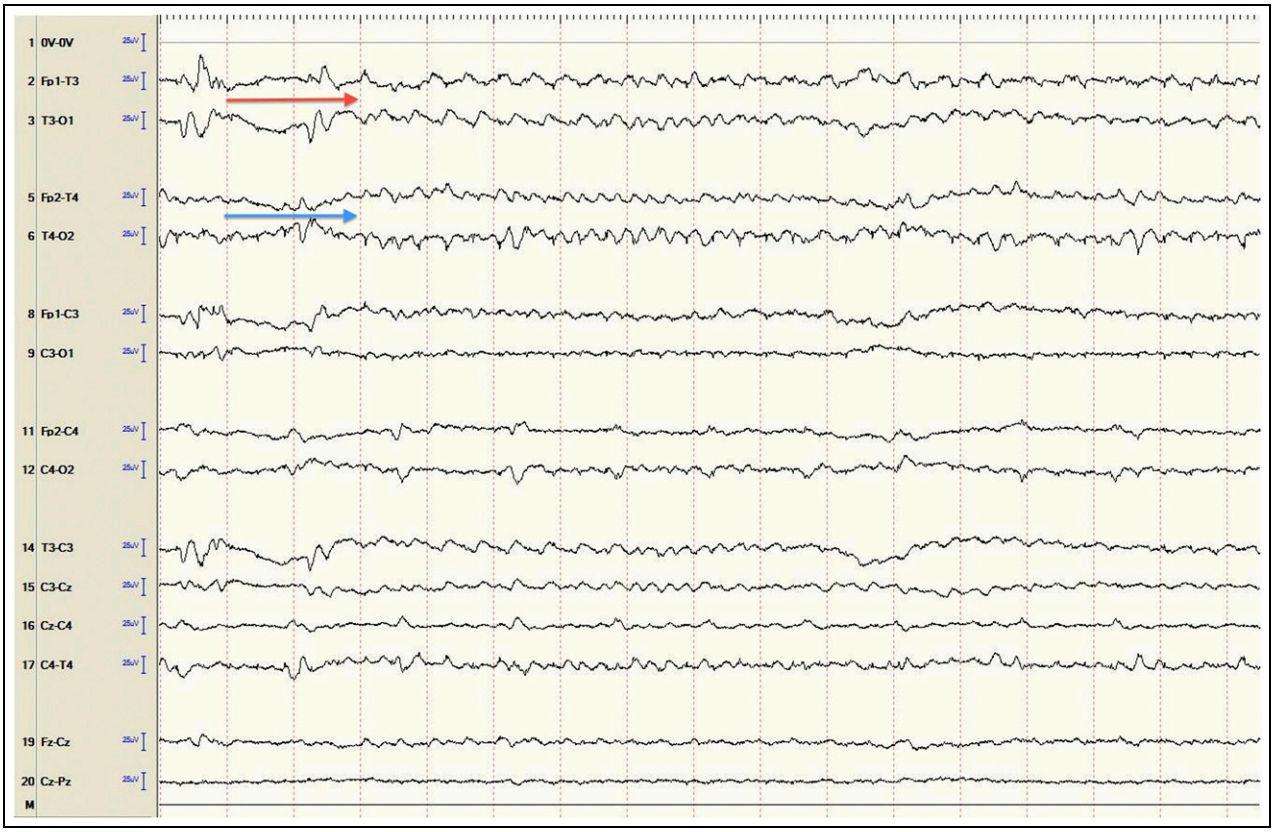

Figure 2. Independent rhythmic ictal discharges from the left temporal region, T3 (top arrow, ~2 Hz), and the right temporal region, T4 (bottom arrow, ~4 Hz). This sample is for a 1-day-old term infant with perinatal asphyxia.

may result in some superficial, subarachnoid hemorrhage with seizures occurring transiently. In more severe cases with signs of trauma such as bruising, seizures may be more persistent. Sinovenous thrombosis also can result in superficial and intraparenchymal bleeding that is symptomatic with seizures. (16) Acute and chronic strokes may present with seizures as well, even if there is no hemorrhagic component. (17) In the setting of stroke or unexplained intracranial bleeding, it may be advisable to look for inherited hemorrhagic or prothrombotic disorders. Encephalitis and meningitis may present with seizures. Both bacterial meningitis (eg, group B β-hemolytic streptococcus) and viral encephalitis (eg, herpes simplex virus) can be causes of seizures. (18)(19)

Congenital brain malformations may manifest with seizures in the neonatal period, although in many cases, particularly with small focal dysplasias and heterotopia, seizures may begin at several months or years of age. Some of the more severe malformations that may manifest with seizures in the neonate are lissencephaly, holoprosencephaly, and varying degrees of hydranencephaly. The malformations often contain neurons that have persistent immature GABAergic function. (20)

There are numerous genetic disorders that can present with seizures. Most often the seizures start days (or weeks) after the infant starts to feed and is no longer regulated by the mother's normal metabolism. Abnormal metabolic intermediates start to accumulate. The usual initial manifestations of these disorders are unexplained encephalopathy and seizures. A detailed review of these disorders is beyond the scope of this review, but consideration of specific causes treatable with dietary restriction or supplementation warrants discussion. Some of the amino acidopathies and organic acidopathies may be amenable to dietary restrictions (ie, restricting branch chain amino acids in maple syrup urine disease). Seizures caused by biotinidase deficiency will respond to biotin supplementation. (21)

The classic but rare cause of unexpected and often early seizures (an exception to the rule of seizures starting a few days after feeding) is pyridoxine dependency and folinic acid–responsive seizures. Seizures often are present

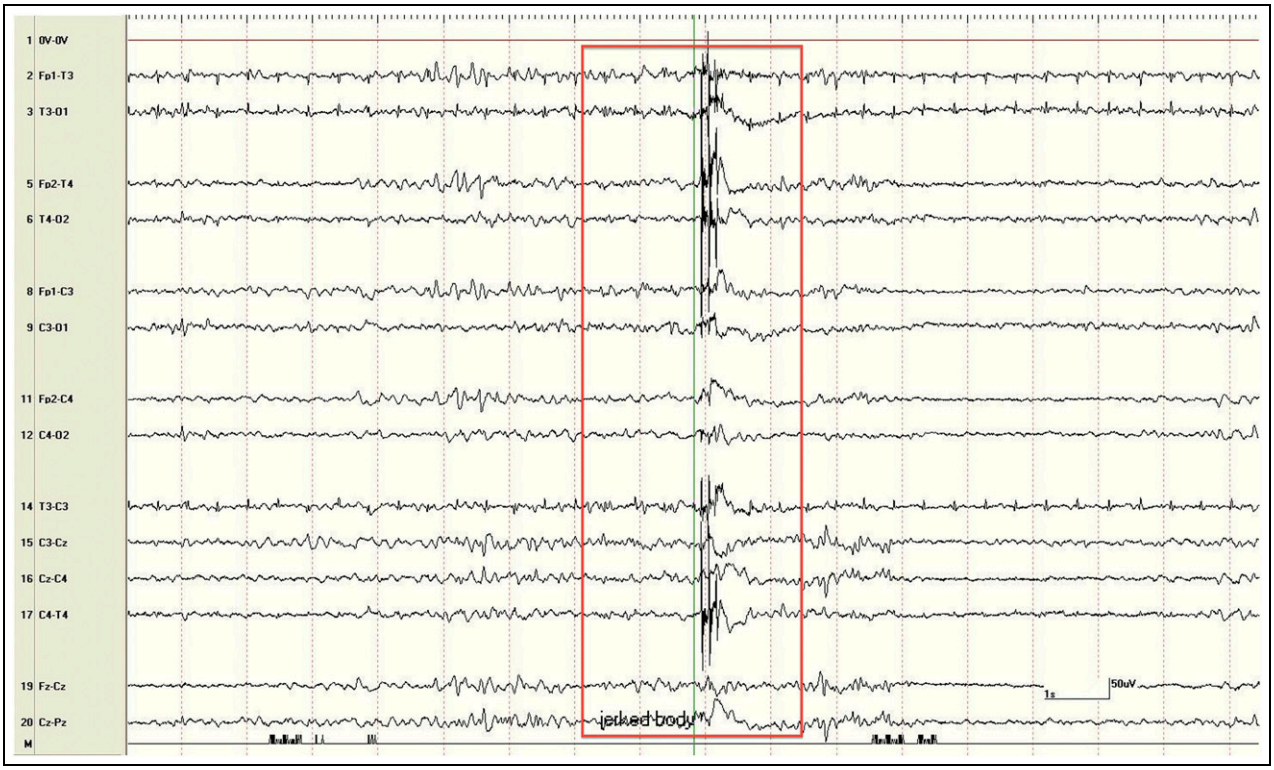

Figure 3. Muscle artifact on EEG, but with no ictal discharge during a myoclonic seizure in a 3-day-old term infant with severe neonatal encephalopathy.

early and occur unexpectedly in infants not known to be at risk. The seizures are usually medically refractory, and the EEG findings are very disorganized. In this setting, an empirical trial of pyridoxine possibly followed by folinic acid may be diagnostic and therapeutic. (22)(23)(24)

There are two well-characterized benign neonatal seizure syndromes: benign familial neonatal convulsions and benign neonatal seizures. The seizures are usually focal clonic seizures that respond easily to antiseizure medication. With benign familial neonatal convulsions, as the name implies, there is a family history of neonatal seizures. The seizures usually remit spontaneously after a few days or weeks. With benign neonatal seizures (so-called Fifth Day Fits because they manifest themselves between 4–6 days of life), there is not a positive family history. The diagnosis is suspected because of the lack of seizure risk factors, an otherwise benign examination, a normal background EEG reading, and a benign clinical course. (25)(26) In both cases, medication can be withdrawn after a few weeks or months.

Early infantile epileptic encephalopathy (EIEE, Otahara syndrome) and early myoclonic encephalopathy (EME) are two very concerning neonatal seizure syndromes. Infants with EIEE usually present with tonic spasms. In EME, as the name implies, myoclonic seizures are a major feature. EEG findings in both usually show a burst-suppression pattern or other very abnormal background. For both syndromes, the prognosis for a normal outcome is poor. EME is most often a manifestation of an underlying genetic-metabolic disorder. (27) EIEE is more often a manifestation of a serious cerebral malformation. (28)

Diagnostic Studies

EEG Readings

EEG study is used primarily to determine the risk of seizures in a given patient and whether seizures are occurring during the EEG reading. Unlike in older children and adults, "sharp waves" or "spikes" occurring in isolation in the EEG study of a neonate are not indicative of significantly increased risk of seizures. Instead, an excess of sharp waves is considered a nonspecific indicator of encephalopathy. Bursts of repetitive or short, stereotyped evolving rhythmic bursts of sharp waves (brief electroencephalography rhythmic discharges) are more supportive of an increased seizure risk (Fig 4). (29)

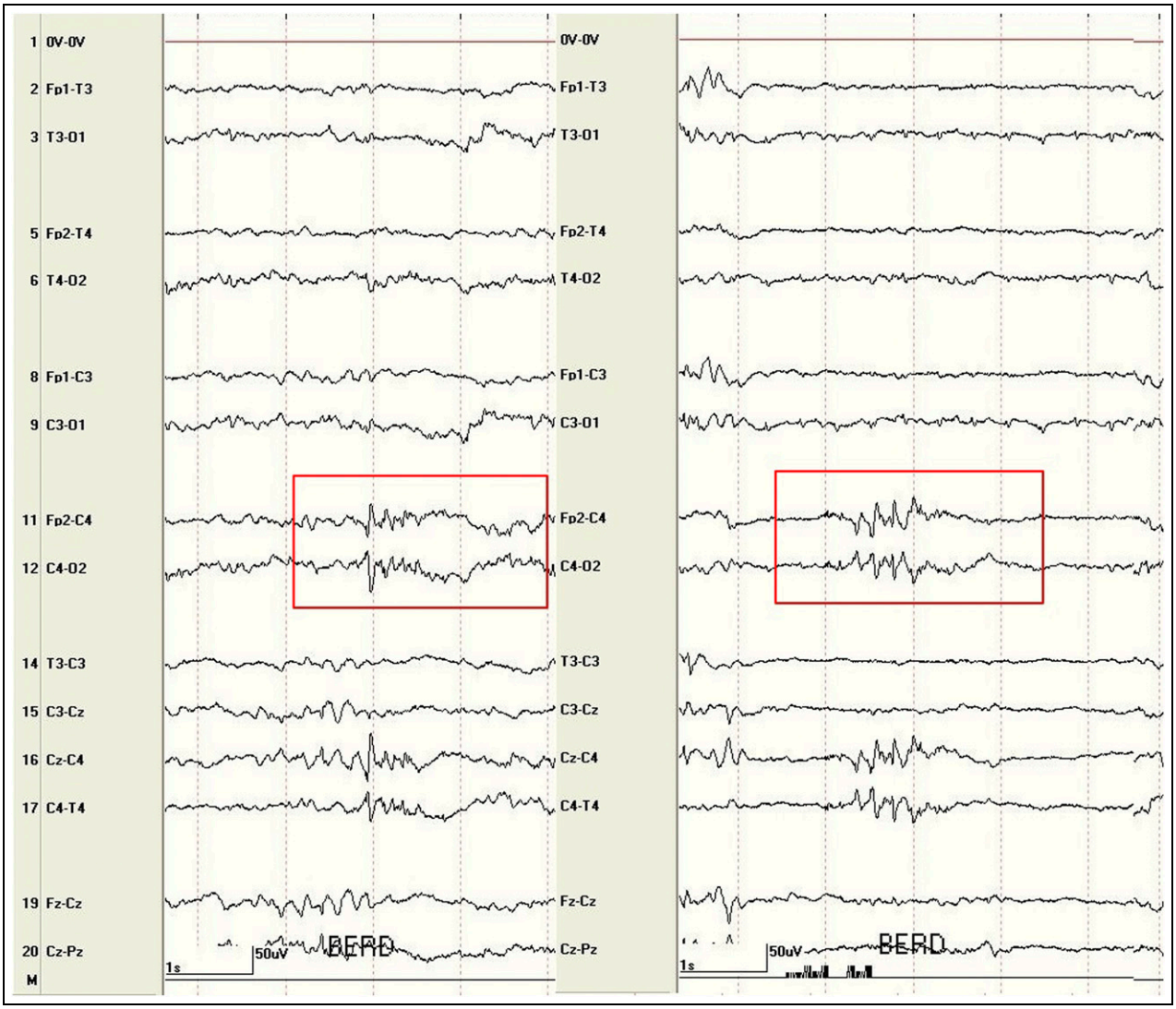

Figure 4. Brief electroencephalogram rhythmic discharges (BERDs) in the right central region (C4, boxes) of a 2-day-old term infant with moderate to severe neonatal encephalopathy. Later in the recording, a focal clonic seizure occurred with left leg rhythmic movements.

Evolving rhythmic discharges longer than 10 seconds typically are identified as seizures and not brief electroencephalography rhythmic discharges. Neonates often have electrographic seizures without corresponding ictal behavior. (30) Seizures on EEG, but without obvious clinical signs, are sometimes colloquially referred to as "subclinical" seizures, although "electrographic seizures" is a more accurate designation. A fairly common scenario is for clinically apparent seizures to be controlled after administration of seizure medication, only to find that the EEG reading shows frequent (or sometimes continuous) electrographic seizures. (11)

Long-term EEG readings (>1 hour) often are used to monitor for seizures in infants who have unusual paroxysmal behavior suggestive of seizures but not sufficiently clear from a bedside observation perspective to warrant loading with an antiseizure medication. In such cases, long-term EEG monitoring with simultaneous video recording usually provides an answer as to the epileptic versus nonepileptic nature of such behaviors, assuming they occur often enough to be recorded.

The other scenario in which continuous EEG monitoring can be useful is when infants are very sick or pharmacologically paralyzed, such that there is concern their

condition will mask frequently occurring seizures. (31) (32) In these cases, otherwise unexplained variations in blood pressure, heart rate, and oxygen saturation may raise the question of subtle seizures. The mere presence of some brief, self-limited seizures is of uncertain clinical significance, but most practitioners treat very frequent or continuous electrographic seizures even in the absence of clinical signs.

Amplitude-integrated EEG monitoring is a technique used to follow the EEG state of the infant and to provide a means of early recognition of changes in cerebral function. It consists of a graphic display of EEG frequency and amplitude information from a limited number of scalp electrodes (usually two to four). Certain changes in the tracing can suggest the occurrence of seizures, but it is important to correlate such changes with routine EEG tracings. (33)

MRI (Ultrasonography and Computed Tomography)

Neuroimaging is a valuable tool for defining structural abnormalities that may be etiologies of seizures such as cerebral malformations and strokes. Hemorrhage and signs of asphyxial injury may be apparent. (34)(35)(36) MRI is the most sensitive modality and often reveals subtle cortical malformations not evident on cranial ultrasound or computed tomography (CT). Ultrasonography is very accessible and much less invasive for infants in the NICU but is insensitive for more subtle cortical malformations. CT and MRI scanning usually involve transportation out of the NICU to obtain the imaging study, but acquisition times are faster with computed tomography than MRI, decreasing the need for sedation and speeding the sick infant's return to the intensive care suite.

Treatment

Most of the data for treatment of neonates with seizures come from studies and reports in term or near-term infants. Much less is known about any differences in efficacy and adverse effects in very premature infants. Differences in renal function and hepatic function in very low birth weight infants should prompt conservative antiseizure medication dosing, and when available, following of drug serum concentrations.

ACUTE TREATMENT OF METABOLIC DERANGEMENTS. The first priority when beginning to treat the neonate with seizures is to ensure that there is adequate oxygenation and cardiac function. Once these basic things are addressed, there needs to be rapid assurance that the infant is not hypoglycemic, hypocalcemic, hypomagnesemic, or hyponatremic. Correction of these metabolic derangements will either control the seizures or "allow" the seizure medications to be effective.

PHENOBARBITAL. Phenobarbital has long been a mainstay of seizure treatment in the neonate. Administration intravenously can be accomplished quickly once intravenous access is obtained, serum concentrations can be determined rapidly, and further doses can be administered to achieve a desired value. The enteral formulation is well absorbed, so transition from parenteral to oral solution is typically simple to achieve. Phenobarbital typically is given as a loading dose of 15 to 20 mg/kg. In cases of an acute, transient seizure-provoking insult, maintenance treatment may not be needed. If, however, seizures recur after loading, or if there is a perceived chronic seizure-provoking etiology, maintenance dosing is initially 3 to 4 mg/kg per day divided into two daily doses. Phenobarbital is metabolized in the liver, so maintenance dosing often needs to be increased to the range of 5 to 8 mg/kg per day because infants mature and recover from acute liver dysfunction after asphyxia. (37) Hypothermia also decreases phenobarbital metabolism.

PHENYTOIN/FOSPHENYTOIN. Phenytoin is as effective for initial seizure control as phenobarbital. (38) Because the transition to enteral administration is often challenging owing to difficulty sustaining therapeutic serum concentrations, many infants are treated initially with phenobarbital. Another disadvantage of phenytoin compared with phenobarbital is the much higher protein binding. There may be drug-drug interactions with other highly protein-bound medications. On the other hand, a loading dose of phenytoin is less likely than phenobarbital to cause sedation. Phenytoin typically is given as a loading dose of 15 to 20 mg/kg followed by maintenance doses ranging from 5 to 8 mg/kg per day divided into two daily doses. Phenytoin is poorly soluble at neutral pH, and it precipitates in solution with dextrose, so it must be given in dextrose-free intravenous solutions. The vehicle is also very irritating and can cause soft tissue injury when it extravasates. Fosphenytoin is more soluble at neutral pH, is less irritating to soft tissue, and can be administered faster than phenytoin without as great a risk of bradycardia. (39)(40) The loading dose for fosphenytoin is essentially the same as for phenytoin because it is dosed in "mgPE" for "phenytoin equivalents." Phenytoin's antiepileptic mechanism is sodium channel blockade: it reduces repetitive neuronal firing.

When adding a second antiseizure medication to a child's treatment regimen, it is reasonable to use a drug with a different mechanism of action than that of the initial drug. For this reason, phenobarbital and phenytoin, with their respective inhibition-enhancing and excitation-suppressing mechanisms, have long been used in combination when neonatal seizures prove refractory to initial monotherapy.

BENZODIAZEPINES. The three commonly used parenteral benzodiazepines are midazolam, diazepam, and lorazepam. (41)(42)(43) All are effective antiseizure medications, although controlled trials in neonates are lacking. Lorazepam has the longest duration of action among these three medications. Midazolam and diazepam have a slightly faster onset of action because of greater lipid solubility, but they redistribute out of the brain more quickly than lorazepam. In the acute seizure setting, when the need for maintenance antiseizure medication therapy is uncertain, stopping the seizure with a benzodiazepine then assessing the situation may be the best balance between efficacy, safety, and prevention of longer-duration, drug-induced sedation. In older children, rectal administration of diazepam and nasal administration of midazolam are often effective in the absence of intravenous access. Again, data for neonates are sparse. For lorazepam, the usual dose for acute treatment of seizures is 0.05 mg/kg, repeated once in 15 to 20 minutes if the initial dose is not efficacious.

OTHER MEDICATIONS. Many other seizure medications often prescribed for older children have been reported as being used in neonates, typically in small case series. (44) Among all these medications, levetiracetam has been adopted with some enthusiasm, despite the lack of controlled trials in neonates. (45)(46)(47) It has no drug-drug interactions, and it is not metabolized in the liver. It is also available as an oral solution, making conversion from parenteral to oral/enteral maintenance dosing fairly easy. Its exact mechanism of action remains uncertain, but it does not act via direct modulation of inhibitory or excitatory neurotransmission. Numerous case series indicate its efficacy and absence of serious side effects. There is no standard dosing regimen for neonates, but described approaches range from an initial loading dose between 10 and 50 mg/kg and daily maintenance doses in a similar range (divided into twice-daily dosing). (46)(47)(48) Because it is excreted in the urine, infants with renal dysfunction need lower doses.

WITHDRAWAL OF TREATMENT. In many cases, neonatal seizures occur over a fairly brief period. Particularly in the setting of an acute insult such as mild trauma or mild to moderate asphyxia, the seizures may remit in a few days or weeks. In such cases, an initial single loading dose of an antiseizure medication followed by observation may be reasonable. In other cases, maintenance therapy with antiseizure medications may be discontinued in a few days. Even with more significant initial injuries, infants whose seizures have been well controlled may be tried off medication a few weeks or a few months after discharge.

Prognosis

Seizures are a marker of increased risk for an abnormal neurologic outcome. Estimates for morbidity vary greatly among published series but generally range between 35% and 60%. There is an increased risk of cerebral palsy, abnormal cognitive outcome, and epilepsy. (49)(50)(51)

Neonatal seizures are regarded largely as a marker of brain injury. It has proven very difficult to define whether the seizure burden alone, independent of the underlying etiology and severity of the brain injury, contributes significantly to the functional outcome. For this reason, the degree of aggressiveness of intervention for brief, self-limited, and infrequent electrographic seizures without clinical signs remains uncertain. It is generally accepted that adding a second medication (eg, adding phenytoin to phenobarbital) to try to achieve better control of electrographic seizures is associated with a relatively low risk. But once one adds additional medications (eg, benzodiazepines), the risk of hypotension and the attendant risk of decreased cerebral perfusion must be weighed carefully.

American Board of Pediatrics–Perinatal Medicine Content Specifications

- Understand the spectrum of clinical seizures in the newborn infant.
- Understand the differential diagnoses and evaluation of neonatal seizures.
- Understand the management and prognosis of neonatal seizures.

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NeoReviews Quiz
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™*. In order to successfully complete 2012 *NeoReviews* articles for *AMA PRA Category 1 Credit™*, 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 12-hour-old infant born at 26 weeks' gestation has a hypoglycemic-induced seizure. In contrast, a 1-month-old infant with the same degree of hypoglycemia does not have a seizure. Of the following, the most likely reason for a premature infant to be more prone to seizure activity than an older infant is a(n):
   A. decrease in the excitatory effect of γ-aminobutyric acid (GABA)
   B. enhanced neuronal secretion of calcium
   C. greater concentration of chloride in the neuron
   D. higher amount of intracellular neuronal ATP
   E. increased amount of GABA inhibitors

2. A nurse in the newborn nursery is concerned that a 2-hour-old infant might have seizure activity. The infant's prenatal course was benign and he was born by emergent cesarean delivery following a late fetal heart rate deceleration. After birth, the infant had a short period of apnea that required positive-pressure ventilation for a few minutes. Upon arrival to the newborn nursery, the nurse observed rapid jerking of his right ankle for 5 seconds while he was crying. After plantar flexing his right foot, the movements resolved. Of the following, the most likely cause of this infant's jerky movements is:
   A. benign sleep monoclonus
   B. focal clonic seizure
   C. jittery movement
   D. limb clonus
   E. subtle motor seizure

3. A 12-hour-old full-term infant has episodic stiffening and posturing of the left leg that does not resolve with repositioning of the leg. These movements are sometimes associated with eye deviation and head turning and correlate with epileptiform rhythmic discharges on an electroencephalogram. Of the following, this neonatal seizure is most likely classified as a:
   A. focal clonic seizure
   B. focal tonic seizure

C. generalized tonic seizure
D. myoclonic seizure
E. subtle seizure

4. A full-term female infant presents at age 5 days with a focal-clonic seizure. Her antepartum and postnatal courses are benign. The infant's physical examination is normal, and her vital signs remain stable during the seizure. There is no family history of neonatal seizures. The infant's electroencephalogram shows epileptiform activity during the seizure period but has a normal background pattern. She receives phenobarbital for 4 months, and the seizure activity does not recur. Of the following, this infant's most likely diagnosis is:

A. benign neonatal seizure
B. biotinidase deficiency
C. Ohtahara syndrome
D. pyridoxine deficiency
E. subtle autonomic seizure

5. A term male infant is receiving therapeutic hypothermia after severe perinatal depression. He has a generalized tonic seizure at age 16 hours. The neonatology fellow is teaching the pediatric resident about the risks and benefits of phenobarbital and phenytoin. Of the following, the most likely rationale for initially treating this infant with phenobarbital instead of phenytoin is:

A. A loading dose of phenobarbital is less likely to cause sedation.
B. Phenobarbital has lower protein-binding and fewer interactions with other medications.
C. Phenobarbital is more effective for initial seizure control.
D. Phenobarbital is not metabolized by the liver.
E. Therapeutic hypothermia has no effect on phenobarbital metabolism.

Neonatal Seizures

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