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Etiology of Neonatal Seizures

Jin S. Hahn, MD,* Donald M. Olson, MD*

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

1. Name the primary causes of neonatal seizures today.
2. Describe the cerebral malformations associated with neonatal seizures.
3. Name the metabolic disorders that are associated with neonatal seizures.
4. Compare the characteristics of familial or idiopathic epilepsies.
5. List appropriate diagnostic tests for neonates who have seizures.
6. Provide a prognosis based on the cause of neonatal seizures.

Introduction

Neonatal seizures are a common problem in the newborn nursery and can occur in infants at any gestational age. Seizures in a newborn infant evoke a sense of urgency among neonatologists because they often indicate a disturbance of the central nervous system (CNS). Causes of neonatal seizures encompass virtually the entire spectrum of neurologic disorders of infancy, but most neonatal seizures today are due to hypoxic-ischemic brain injury and intracranial hemorrhage.

The proper treatment of neonatal seizures depends on the cause. For example, neonatal seizures due to a transient metabolic disturbance, such as hypocalcemia or hypoglycemia, are treated by correcting the underlying metabolic derangement. However, seizures due to such transient disturbances are relatively infrequent today because of improved neonatal care. For neonates who have seizures caused by a systemic infection (sepsis) or CNS infection (meningitis and encephalitis), the underlying infection must be treated appropriately. The specific cause also has prognostic implications.

More common etiologies of neonatal seizures are discussed in this review (Table 1). As discussed in the review on neonatal electroencephalography (EEG) in this issue of NeoReviews, proper identification of epileptic seizures is important. The most common seizure types are: focal or multifocal clonic, tonic, and myoclonic and subtle. Subtle seizures comprise a variety of motor and autonomic phenomena and are more common in neonates who have severe encephalopathies. However, neonates often have abnormal paroxysmal motor activity, such as oral-buccal-lingual movements, pedaling, stepping, and rotatory arm movements, that are not associated with ictal EEG patterns. These nonepileptic events do not require treatment with anticonvulsants. The EEG is of particular value for detecting subclinical seizures (EEG seizures without clinical manifestations) and for distinguishing subtle seizures from nonepileptic behaviors.

Hypoxic-Ischemic Encephalopathy

In today’s neonatal intensive care units, hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures. Approximately two thirds of all neonatal seizures are due to this cause.

Infants who have a mild degree of encephalopathy often experience variable levels of consciousness in which periods of lethargy alternate with periods of irritability and “hyperalertness.” They manifest jitteriness, which is described best as a spontaneous or stimulus-induced myoclonus (nonepileptic). Muscle tone is normal or increased, and the deep tendon reflexes are hyperactive. Mild encephalopathy usually lasts for fewer than 24 hours. (1)(2)
Within the first postnatal day, the term newborn may progress to moderate encephalopathy with an altered level of consciousness (lethargy or stupor with reactivity) and hypotonia. Seizures that may occur during this stage must be differentiated from other abnormal movements, such as spontaneous myoclonus, hyperactive tendon reflexes with clonus, and jaw clonus.

Severe encephalopathy is characterized by coma, flaccidity, and unresponsiveness to noxious stimuli. (1)(2) Seizures are very common during this stage and occur within the first 24 hours after birth, often within 12 hours. (3) Focal clonic or multifocal clonic seizures often are present. Furthermore, subtle seizures, consisting of eye deviation, subtle posturing, or autonomic changes, frequently accompany more overt seizures. Infants also may have nonepileptic events, such as decerebrate posturing, which is believed to represent a “brainstem release phenomenon” due to forebrain dysfunction. The seizures usually last for several days and may be difficult to control.

The frequency and severity of neonatal seizures due to hypoxic-ischemic encephalopathy usually parallel the grade of the encephalopathy. Seizures are most common during the first week after birth. As the acute encephalopathy resolves, the seizures also remit spontaneously. Approximately one third of affected infants experience postneonatal seizures (ie, epilepsy).

### Infections

#### Meningitis

Bacterial meningitis can cause seizures that usually occur in the latter part of the first postnatal week. (3) The most common bacterial pathogens are group B *Streptococcus*, *Escherichia coli*, and other gram-negative rods. Approximately 25% of neonates who have bacterial sepsis develop meningitis. (4) Lumbar puncture for cerebrospinal fluid analysis and culture is performed when meningitis is suspected. The degree of EEG background abnormalities, the presence of EEG-documented seizures, and the level of consciousness are strong predictors of outcome. (5)

#### Encephalitis

Various viruses, such as herpes simplex virus (HSV) and enteroviruses, may cause acute encephalitis and seizures. Congenital infections, such as toxoplasmosis and cytomegalovirus infection, may cause seizures, but such seizures tend to occur later in the neonatal period or early infancy.

HSV encephalitis is one of the common severe viral encephalitides in the neonatal period. Seizures due to HSV infection occur in 57% of newborns who have CNS disease and 22% of those who have the disseminated form of disease, but rarely in the skin-eye-mouth (SEM) disease group. (6) The mean age of patients who have CNS disease at initiation of antiviral therapy is 15 to 20 days. (6) However, approximately 10% of patients exhibit onset of symptoms within the first 24 hours after birth, suggesting in utero acquisition of HSV infection. In the CNS and disseminated forms of the infection, typical skin vesicles are absent in approximately 40% of infants. (6)

The neonatal form of HSV encephalitis is caused more often by type 2 HSV that the newborn acquires during delivery from maternal genital lesions. Fetal scalp moni-
toring may be a risk factor for acquiring the virus. Neuroimaging studies in neonatal HSV encephalitis often show diffuse brain abnormalities. In severe CNS disease, EEG may show a characteristic multifocal periodic or pseudoperiodic pattern. (7) The periodic sharp activity (recurring at 1- to 4-sec intervals) appears in the temporal, frontal, and central regions. It usually does not vary and is interrupted only by focal seizures. Since the introduction of acyclovir therapy, severe CNS disease occurs rarely, and more nonspecific EEG abnormalities usually are recorded. (8) HSV encephalitis should be considered in the differential diagnosis of acutely ill newborns who have seizures. If the presentation is compatible with neonatal HSV infection, appropriate diagnostic studies should be obtained and acyclovir treatment initiated. HSV cultures from the conjunctivae provide the greatest yield, although skin and oropharyngeal samples often also are obtained. (6) HSV DNA polymerase chain reaction (PCR) of CSF specimens appears to be sensitive for CNS involvement, but CSF viral cultures have a low yield.

### Intracranial Hemorrhage

Subarachnoid hemorrhages may cause neonatal seizures in the term infant. This often occurs in the context of a vaginal delivery of an infant who otherwise appears fairly healthy. Seizures often begin during the second day after birth. Computed tomography (CT) and magnetic resonance imaging (MRI) may show subarachnoid blood in the posterior fossa, over the cerebral convexities, or both. Blood collections also may be present along the tentorium. These seizures are usually self-limited and have a good prognosis.

In the preterm infant, intraventricular hemorrhages may result from bleeding in the subependymal germinal matrix. Large hemorrhages often are associated with periventricular ischemic lesions and may cause seizures. Seizures may manifest as generalized tonic posturing or subtle seizure phenomena. (3) In one study, seizures due to intraventricular hemorrhages accounted for 45% of the preterm infants who had EEG-documented seizures. (9) However, in our experience, seizures due to catastrophic intraventricular hemorrhages in preterm infants seem to be less common.

Intraventricular hemorrhage in term infants may result from trauma, hypoxic-ischemic injury, or venous sinus thrombosis. In term infants, the hemorrhages usually originate in the choroid plexus. Seizures may occur in affected infants, and the duration of seizures and prognosis appear to be related to the cause of the hemorrhage.

Seizures may occur from subdural hemorrhages, which usually are the result of trauma. CT and MRI reveal subdural collections of blood over the convexities and along the tentorium. There also may be a component of subarachnoid hemorrhage. Seizures occur within the first 48 postnatal hours. (3)

### Cerebrovascular Infarction (Stroke)

Cortical injury may result from occlusion of an artery that causes necrosis of all cellular elements in the distribution of a single vessel. The middle cerebral artery is involved most frequently. Most injuries are believed to be due to embolic or thrombotic processes. Although the actual cause is found infrequently, coagulopathy, congenital heart disease, and trauma are common associated disorders. As the infarction evolves, brain parenchyma dissolve and a cavity (porencephalic cyst) forms. If multiple vessels are involved, multicystic encephalomalacia or hydranencephaly may result. Clinical features are understandably variable because the time of the infarction and the location are the primary determinants of physical findings.

Seizures frequently are described in infants who have neonatal strokes. (10) Focal clonic seizures are common. Hemiparesis may be present on neurologic examination, but it often is subtle. The EEG usually demonstrates lateralized abnormalities and allows assessment of the severity of the encephalopathy in other cortical regions. CT and MRI show a wedge-shaped area of abnormal signal that is in the distribution of a single artery. MRI sequences using diffusion-weighted images may provide a sensitive method of detecting infarcts early in the course before CT or routine MRI sequences reveal the lesion.

Infants may develop spastic hemiparesis ("hemiplegic cerebral palsy") as a long-term sequela. Because of the frequent involvement of the middle cerebral artery, the upper extremity is more impaired. The extent and location of the pathologic lesion are important factors in determining whether intellectual impairment and epilepsy also develop. (11)

Cerebral venous thrombosis often presents in newborns who have seizures, respiratory distress, and lethargy. (12)(13) In one study, 68% of neonates who had cerebral venous thrombosis experienced seizures. (13) The occlusions usually occur in the superior sagittal sinus, sigmoid/transverse sinus, or multiple venous sinuses. Venous occlusions may lead to focal cerebral injury (ie, strokes), which frequently are hemorrhagic. MRI has been particularly useful for diagnosing venous sinus thrombosis and focal injury due to venous occlusions. (12) Venous sinus thrombosis also may cause...
secondary intraventricular (choroid plexus) hemorrhages in the term newborn. Risk factors for venous thrombosis include persistent pulmonary hypertension, infection, dehydration, and thrombophilic disorders.

Extracorporeal membrane oxygenation (ECMO) is associated with various cerebrovascular disturbances in addition to the underlying hypoxic condition that necessitates its use. (14) Posterior fossa hemorrhages have been noted in infants receiving ECMO, presumably due to disturbance of cerebral venous return. Seizures are relatively common in infants undergoing ECMO. (15)

Cerebral Malformations
Cerebral malformations are well-recognized causes for seizures during infancy and the newborn period. Those that typically present in the neonatal period are discussed here.

With holoprosencephaly, there is failure of complete separation of cerebral hemispheres and deep gray nuclei, often associated with a fluid-filled dorsal cyst. Seizures occur in approximately 50% of patients who have holoprosencephaly, and more severe epilepsies occur in those who have additional dysplastic cortical abnormalities. (16) EEG recordings from scalp regions overlying the abnormal telencephalon often appear grossly abnormal, displaying multifocal spikes and polyspikes; prolonged runs of rhythmic alpha, theta, or delta activity; asynchrony; and a fast beta activity that probably represents subclinical seizures.

Lissencephaly (agyria-pachygyria) is a developmental malformation in which the cortical surface of the brain is smooth or contains broad, thick gyri. Seizures are commonly associated with various cerebrovascular disturbances in addition to the underlying hypoxic condition that necessitates its use. (14) Posterior fossa hemorrhages have been noted in infants receiving ECMO, presumably due to disturbance of cerebral venous return. Seizures are relatively common in infants undergoing ECMO. (15)

Transient Metabolic Disorders
Hypoglycemia
Seizures due to hypoglycemia occur most commonly in infants of diabetic mothers or infants who are small for gestational age. Seizures may be focal and often begin on the second postnatal day. The hypoglycemia may be due to other conditions, such as hypoxic-ischemic encephalopathy or infections. Correction of the hypoglycemia treats the seizures and concomitant neurologic symptoms such as jitteriness, hypotonia, and lethargy. In cases of persistent hypoglycemia, further metabolic and endocrinologic evaluations should be considered.

Hypocalcemia
Hypocalcemia was a commonly reported cause of seizures in the past, constituting 20% to 34% of neonatal seizures in the 1960s and early 1970s. (19) Most affected infants experienced late-onset (age 4 to 14 d) hypocalcemic seizures that were due to the high phosphate content of cow milk formulas. This nutritional problem has become rare as careful attention is paid to the calcium: phosphorous ratio in infant formulas. Today, hypocalcemic seizures are uncommon (constituting approximately 3% of the total) and are of early onset (first 3 d). (20) The cause of hypocalcemia also has changed, with approximately 50% of cases being associated with congenital cardiac defects. (19) Prematurity and endocrine dysfunctions (maternal hyperparathyroidism or idiopathic hypoparathyroidism) are some of the causes of hypocalcemia. Hypomagnesemia often is associated with hypocalcemia, but it does not seem to cause seizures in isolation without hypocalcemia.

A diagnostic evaluation for DiGeorge or velocardiofacial syndrome (22q11.2 deletion syndrome) should be considered for patients who present with hypocalcemia and cardiac disorders. A fluorescent in situ hybridization test for deletion in 22q11.2 is the diagnostic method of choice. Affected patients also have craniofacial abnormalities, hypoparathyroidism, and immune deficiencies.

Hypocalcemia also may be induced after cardiopulmonary bypass and blood transfusion. (19) It is important to provide adequate supplementation of calcium postoperatively in patients who have undergone open-heart surgery.

Similarly to seizures due to hypoglycemia, those due to hypocalcemia may be focal.

Persistent Metabolic Disorders
Inborn Errors of Metabolism
Inborn errors of metabolism of the newborn often are associated with encephalopathy and seizures. A variety of
such disorders may cause neonatal seizures, including urea cycle defects, organic acidurias, and aminoacidoplasies. Hyperammonemia and metabolic acidosis are signs of such disorders. Rare causes include disorders of biotin metabolism, peroxisomal disorders, molybdenum cofactor deficiency, sulfite oxidase deficiency, and disorder of fructose metabolism. (21) These disorders should be suspected when an encephalopathy develops in a healthy infant who deteriorates after the initiation of feedings. The goal is to identify the metabolic problem and correct the underlying defect whenever possible while administering anticonvulsants.

In the neonatal form of maple syrup urine disease and propionic acidemia, a characteristic EEG pattern is evident in the first few postnatal weeks. (22) Runs and bursts of 5 to 7 Hz, primarily monophasic negative (mu-like or comblike) activity in the central and midline central regions are present during all states, with the most abundant bursts occurring in non-rapid eye movement sleep. The pattern gradually disappears after the institution of dietary therapy.

Classic nonketotic hyperglycinemia (glycine encephalopathy) is due to a defect in cleavage of the excitatory amino acid glycine. This lifelong condition usually causes neonatal seizures characterized by early myoclonic encephalopathy and severe static encephalopathy. Transient nonketotic hyperglycinemia is a very rare disorder characterized by clinical and biochemical findings similar to those seen in classic nonketotic hyperglycinemia. (23) Abnormalities in amino acids resolve partially or completely in days to months. Nearly all patients who have the classic nonketotic hyperglycinemia develop severe neurologic sequelae; most patients who have the transient form exhibit normal development. Therefore, distinguishing the transient from the classic form of nonketotic hyperglycinemia is important for prognosis. CSF analysis of glycine may be needed to diagnose either form.

Pyridoxine-dependent Epilepsy
Pyridoxine-dependent epilepsy (PDE) is caused by an inborn abnormality in pyridoxine-dependent synthesis of the inhibitory neurotransmitter GABA. This is a rare autosomal recessive disorder. Children present with frequent seizures or status epilepticus in the newborn period or early infancy. Seizures are refractory to conventional anticonvulsants. The seizures may develop in utero. The seizures are controlled only with the administration of high-doses of pyridoxine (vitamin B6). In between the seizures, the infants are hypotonic, agitated, and irritable. They have exaggerated startle responses.

The seizures often are partial in onset and generalize secondarily. Myoclonic seizures and infantile spasms also may occur. The interictal EEG shows a burst-suppression pattern and generalized rhythmic slow waves. (24)

No routine diagnostic tests are available to confirm this diagnosis. For newborns and infants who have medically refractory seizures, PDE should be considered in the differential diagnosis. The diagnostic test (and treatment) consists of a trial of pyridoxine (100 mg, intravenous bolus). This usually is infused over several minutes because a rapid bolus may induce apnea, bradycardia, and severe hypotonia. Simultaneous EEG monitoring during administration is helpful to determine a response, which may require 5 to 10 minutes. If there is a response to pyridoxine, the infant should be treated with daily therapy of 200 mg/d orally. Other antiepileptic medications can be withdrawn gradually. A pyridoxine withdrawal challenge can confirm the diagnosis. If the child has PDE, seizures recur in 7 days to 3 weeks, and pyridoxine should be restarted.

Although the seizures may be controlled with pyridoxine, psychomotor retardation is common in children who have PDE. The spectrum of dysfunction varies from mild to severe. Even early diagnosis and treatment does not seem to prevent the development of mental deficiencies. In some children, progressive ventricular enlargement has been noted in serial neuroimaging studies. (25)

Glucose Transporter Type 1 Deficiency
Infants who have glucose transporter type 1 deficiency syndrome (GLUT-1 DS) may have neonatal seizures, but seizures appear more frequently during infancy (usually between 6 and 12 wk). This disease is due to GLUT-1 deficiency, which results in decreased transport of glucose at the blood-brain barrier and across glial cell membranes. (26) This defect of glucose transport into the brain results in hypoglycorrhachia (CSF glucose concentrations are very low, usually <40 mg/dL [2.2 mmol/L]) that causes epilepsy, developmental delay, and a complex motor disorder in early childhood. Several mutations have been identified in the GLUT-1 gene. The diagnosis should be suspected when there is unexplained low CSF glucose concentrations relative to serum glucose levels. GLUT-1 DS can be confirmed by an assay that measures the uptake of $^{14}$C-O-methyl-D-glucose in erythrocytes. (27)

The ketogenic diet, established to treat intractable childhood epilepsy, is effective treatment for GLUT-1 DS. (28) Ketones serve as an alternative fuel for the brain. The diet appears to control epilepsy in affected children, although the long-term outcome is not known. Early
recognition of this disorder is important because there appears to be a correlation between delay in treatment and severity of encephalopathy.

**Familial or Idiopathic Epilepsies**

**Benign Familial Neonatal Convulsions**

The seizures of benign familial neonatal convulsions usually begin during the first week after birth. No other cause is found for the seizures. Findings on the neurologic examination and interictal EEG are normal. The child may have several seizures during infancy, but they resolve spontaneously. There usually is a family history of seizures during the neonatal period or infancy.

There appears to be a characteristic pattern of electroclinical seizures. The seizures begin with a diffuse flattening of the background accompanied by apnea and tonic motor activity. Seizures subsequently evolve to rhythmic slow activity that is followed by bilateral spike and sharp wave discharges during bilateral clonic activity. (29)(30) Vocalizations, chewing, and eyelid movements also are present during this phase. Others have found that the seizures in benign familial neonatal convulsions are focal in onset, with secondary generalization. (31)(32)

Benign familial neonatal convulsions is an idiopathic epileptic syndrome that has an autosomal dominant inheritance with an 85% penetrance. Large familial pedigrees have been identified. In 1989, two gene loci were identified, one on the long arm of chromosome 20 and the other on the long arm of chromosome 8. In 1998, two genes were identified in this syndrome, distinguishing this as the first epilepsy in which a gene was identified. Mutations were found in \( \text{KCNQ2} \) and \( \text{KCNQ3} \), genes for voltage-gated potassium channels. Mutations in \( \text{KCNQ2} \) cause loss or marked reduction in potassium M-current by impairing the repolarization of the neuronal cell membrane. (33) This causes neuronal hyperexcitability.

**Benign Idiopathic Neonatal Seizures (Fifth-day Fits)**

In benign idiopathic neonatal seizures or fifth-day fits, seizures develop between postnatal days 4 and 6 in 80% of patients. The seizures may include focal clonic activity, apnea, and status epilepticus. Children do not have subsequent epilepsy, and development is normal. Family history is negative. The cause of this disorder is unknown.

The interictal EEG in this syndrome shows a theta pointu alternant pattern. The EEG background consists of predominantly sharply contoured theta (4 to 7 Hz) activity that is discontinuous and intermixed with other sharp activity. This pattern persists in awake and sleep states. However, the pattern appears to be somewhat nonspecific; similar patterns can be seen in certain inborn errors of metabolism, such as maple syrup urine disease.

**Early-onset Epilepsies Associated With Encephalopathy**

Early myoclonic encephalopathy is characterized by erratic, fragmentary myoclonic jerks that begin in the newborn period. These jerks are replaced by partial seizures, massive myoclonus, and infrequently, tonic seizures. The EEG shows a characteristic burst-suppression pattern, with periods of suppression (4 to 12 sec) that are seen during sleep. (34) The burst-suppression pattern often evolves into hypersynchronia or multifocal sharp waves and spikes. The infants have marked developmental delay, abnormal tone, and microcephaly. Known causes include inborn errors of metabolism (particularly nonketotic hyperglycinemia), pyridoxine dependency, and brain malformations such as hydranencephaly. The specific cause often is not determined, although familial cases have been reported.

Ohtahara syndrome (early infantile epileptic encephalopathy with suppression-burst) is characterized by frequent tonic spasms that develop in the neonatal period or early infancy. (35) The burst-suppression pattern is seen during sleep and wakefulness. The tonic spasms are associated with the bursts or abrupt attenuation of cerebral activity (desynchronization). Partial seizures are seen in one third of the infants, but myoclonic seizures are rare. The infants have severe encephalopathy and develop intractable epilepsy. The cause varies but often is related to cerebral structural abnormalities, including cerebral dysgenesis, porencephaly, hemimegalencephaly, Aicardi syndrome, and diffuse or focal cortical dysplasias. Less commonly, metabolic disorders are associated with Ohtahara syndrome.

**Timing of Onset of Seizures and Cause**

The timing of seizure onset gives clues about the cause, as suggested by findings from a study in the 1980s. (20) Most seizures due to hypoxic-ischemic encephalopathy and intracranial hemorrhage occurred during the first 4 postnatal days. Hypoxic-ischemic encephalopathy (65% of total) was the most common cause of seizures in both preterm and term infants. Seizures associated with hypoxic-ischemic encephalopathy occurred early in the neonatal period (ie, 90% in the first 2 postnatal days). Furthermore, 80% of all seizures in the first 2 days after birth were related to hypoxic-ischemic encephalopathy. Seizures due to hypocalcemia or hypoglycemia also oc-
occurred within the first 2 days. Most of the seizures due to cerebral dysgenesis occurred after the first week, although a small proportion developed in the first 2 days. There was a bimodal distribution to seizure onset due to infections, with the first peak occurring within the first 4 days and another one occurring after the first week. Seizures due to benign idiopathic neonatal seizures occurred between 5 and 7 days. Those due to benign familial neonatal convulsions tended to occur earlier.

### Diagnostic Evaluations of Neonatal Seizures

Table 2 suggests appropriate diagnostic evaluations for a child who experiences neonatal seizures. The diagnostic approach should be performed in a stepwise manner. Basic chemistry tests, CSF analysis, EEG, and a neuroimaging study should be obtained in nearly all infants who have neonatal seizures. The goal for determining cause is to find any reversible or treatable condition (such as hypocalcemia and hypoglycemia) and to determine the prognosis. The choice of neuroimaging test frequently is debated. If the infant is critically ill or receiving ECMO, bedside cranial ultrasonography may be the study of choice until the child is sufficiently stable for CT or MRI.

Table 2. Diagnostic Evaluations for Neonatal Seizures

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Test Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Tests</td>
<td>● Glucose, electrolytes, calcium, magnesium, ammonia, lactate, arterial blood gases including pH (bedside glucose test if hypoglycemia is suspected)</td>
</tr>
<tr>
<td></td>
<td>● Thrombophilia evaluation when there is evidence of cerebral arterial or venous thrombosis</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>● Cell count, glucose, protein, bacterial culture</td>
</tr>
<tr>
<td></td>
<td>● Herpes simplex virus (HSV) polymerase chain reaction and culture if HSV encephalitis is suspected</td>
</tr>
<tr>
<td></td>
<td>● Lactate and amino acids if inborn error of metabolism is suspected</td>
</tr>
<tr>
<td>Urine</td>
<td>● Toxicology screen, S-sulphocysteine for sulfite oxidase deficiency</td>
</tr>
<tr>
<td>Electroencephalography</td>
<td>● Consider pyridoxine infusion if no obvious cause</td>
</tr>
<tr>
<td>Congenital infection screening</td>
<td>● Serum titers in mother and child</td>
</tr>
<tr>
<td></td>
<td>● Urine culture for cytomegalovirus</td>
</tr>
<tr>
<td>Family history</td>
<td>● Careful family history of neonatal or infantile seizures</td>
</tr>
<tr>
<td>Conjunctiva, skin, oropharynx</td>
<td>● Culture for HSV if HSV encephalitis is suspected</td>
</tr>
</tbody>
</table>


However, cranial ultrasonography is limited in its spatial resolution and ability to assess the cerebral convexities. CT is helpful for identifying acute intracranial hemorrhages or calcifications. MRI is the study of choice for patterns of hypoxic-ischemic brain injury and to identify cerebral dysgenesis.

Excluding infection also is very important. Blood and CSF cultures should be obtained, and the child should receive appropriate antibiotics until bacterial infections are excluded. If there is a clinical indication of viral encephalitis, specifically HSV, a PCR and culture for HSV may be obtained while the child is treated empirically with antiviral agents such as acyclovir.

If no obvious structural or infectious causes are identified, investigations into inborn errors of metabolism should be initiated. A persistent metabolic acidosis suggests an organic acidaemia. Tests for inborn errors of metabolism include ammonia for urea cycle abnormalities, lactate for mitochondrial encephalopathies, serum amino acids, and urine organic acids.

It is crucial to obtain a careful family history of any seizures in family members during the neonatal period or early infancy to assess for familial or genetic epilepsies. Because the seizures of benign familial neonatal convulsions remit during infancy, the parents may not realize that they had experienced early-onset seizures. It is important to query both maternal and paternal grandparents for this history.

### Etiology and Prognosis

The nature and severity of the neurologic process that causes the neonatal seizure is a major determinant of prognosis and outcome (Table 3). For example, approximately 50% of children who have had hypoxic-ischemic encephalopathy with seizures have normal development. (3) Infants whose seizures are due to intraventricular hemorrhages associated with periventricular hemorrhagic infarctions have a low (10%) probability for normal development. Seizures due to subarachnoid hemorrhages are associated with a favorable outcome in most infants. In bacterial meningitis, approximately 50% of the
neonates who have seizures have a normal outcome. (3) Cerebral dysgenesis is associated with a poor outcome. Benign familial neonatal convulsions have a very good prognosis. It is, therefore, important to investigate possible causes of neonatal seizures both to provide meaningful prognostic information and to determine appropriate therapies. In approximately 5% of neonates, no etiology can be determined. (20)

References

Table 3. Causes of Neonatal Seizures and Outcomes

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percent of Patients Who Have Normal Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td>50</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>10</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>90</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
</tr>
<tr>
<td>Early-onset</td>
<td>50</td>
</tr>
<tr>
<td>Later-onset</td>
<td>100</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>50</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>50</td>
</tr>
<tr>
<td>Developmental malformations</td>
<td>0</td>
</tr>
<tr>
<td>Benign familial neonatal convulsions</td>
<td>~100</td>
</tr>
<tr>
<td>Fifth-day fits</td>
<td>~100</td>
</tr>
</tbody>
</table>

35. Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts, Ohtahara syndrome; its overview referring to our 16 cases. *Brain Dev.* 2002;24:13–23

**NeoReviews Quiz**

5. Seizures in newborns can result from several causes. Identifying the cause is important for both treatment and determination of the prognosis. Of the following, the most common cause of neonatal seizures in today’s neonatal intensive care units is:
   A. Central nervous system infection.
   B. Congenital brain malformation.
   C. Drug withdrawal.
   D. Hypoxic-ischemic encephalopathy.
   E. Metabolic disorder.

6. A 2-week-old term newborn has repetitive episodes of myoclonic seizures that are refractory to conventional anticonvulsants. The infant is irritable and hypotonic and has exaggerated startle responses. The electroencephalogram shows a burst-suppression pattern and generalized rhythmic slow waves during the interictal period. After diagnostic testing, you suspect a metabolic disorder. Of the following, the most likely metabolic cause of seizures in this infant is:
   A. Glucose transporter type 1 deficiency.
   B. Maple syrup urine disease.
   C. Nonketotic hyperglycinemia.
   D. Propionic acidemia.
   E. Pyridoxine dependency.

7. The neurodevelopmental outcome for a newborn who has seizures is determined largely by the cause of the seizures. Of the following, a favorable neurodevelopmental outcome is most likely to be associated with:
   A. Bacterial meningitis.
   B. Cerebral dysgenesis.
   C. Hypoxic-ischemic encephalopathy.
   D. Periventricular hemorrhagic infarction.
   E. Subarachnoid hemorrhage.