

REVIEW ARTICLE

NEONATAL SEIZURES; A REVIEW

SH. Fakhraee MD

Abstract:

The occurrence of neonatal seizures may be the first and perhaps, the only clinical sign of a central nervous system (CNS) disorder in the newborn infant. Identifying the etiology for the neonatal seizures is critical to prognosis and treatment. The most common etiology for neonatal seizures is hypoxic-ischemic encephalopathy. Seizures may indicate the presence of a potentially treatable etiology and should prompt an immediate evaluation to determine the precise cause and institute etiology-specific therapy. In this review article, we will discuss the etiology, classification, clinical features, diagnosis and the approaches to treatment of neonatal seizures. **Keywords:** Neonate, Seizure, CNS, Anti-Epileptic drugs (AED'S)

Pathophysiology

A seizure occurs when a large group of neurons undergo excessive, abnormal synchronized electrical discharge (depolarization) within the CNS; depolarization is the result of influx of sodium ions into neuronal cells, whereas repolarization occurs when potassium ions are pumped out of the cells creating the normal negative electrical potential across the cell membrane. This electrical potential is maintained by a sodium-potassium pump, which requires ATP as its energy source. Excessive depolarization is generally felt to be the end common pathway by which seizures occur. Hypoxia-ischemia, the most common cause of neonatal seizures, results in a sharp decrease in energy production, causing a failure of the sodium-potassium pump.

Classification of neonatal seizures

Neonatal seizures are difficult both to identify and to classify. Most seizures in the neonate are focal, the features being subtle and not easily recognizable. Also, newborns rarely have generalized tonic-clonic seizures or partial seizures with rapid secondary generalization. The several types of neonatal seizures as described by Volpe (1) are subtle seizures, clonic seizures (focal or multifocal), tonic seizures, and myoclonic seizures.

Subtle seizures

Subtle seizures are more common in full term than in premature infants. Subtle seizures, such as bicycling movements, lip smacking, roving eye movements, and apnea, are seen more commonly in preterm than in term infants. The most common manifestations of subtle seizures in both preterm and full term infants are ocular movements (1-3); in full term infants, there is usually horizontal sustained deviation

Professor of Neonatology, Mofid
Childrens' Hospital, Shaheed
Beheshti University of Medical
Sciences

Corresponding Author:

S.H Fakhraee MD

Tel:+ 98 21 22251736

Fax:+ 98 21 22251736

Email: shfakhraee@aap.net

of the eyes, whereas in preterm infants, the ictal manifestation is most commonly sustained eye opening, with unresponsiveness and ocular fixation. Other examples include chewing or other oral-buccal lingual movements, pedaling or other stereotypic limb movements, autonomic phenomena, and apneic spells. Video EEG studies have demonstrated that most subtle seizures are not associated with electrographic seizures (4, 5).

Clonic seizures

Clonic seizures can either be focal or multifocal. These movements, most commonly associated with electrographic seizures, often involve one extremity or one side of the body. The rhythm of the clonic movements is usually slow, 1-3 movements per second. These seizures are more typically seen in term infants than in preterm infants.

Tonic seizures

Tonic seizures represent a mixed group-some are probably secondary to brain stem injury/dysfunction, whereas others have distinct EEG correlates on surface EEG monitoring. These may involve one extremity or the whole body; focal tonic seizures involving one extremity often are associated with electrographic seizures.

Myoclonic seizures

Myoclonic seizures are seen in both preterm and term infants and may occur focally in one extremity or in several body parts (multifocal myoclonic seizures). They may or may not have EEG correlates. If the myoclonus is related to sleep or hypoxic – ischemic injury, there is usually no EEG correlate (1, 2, 4). Focal and multifocal myoclonic seizures typically are not associated with electrographic correlates.

Jitteriness

Jitteriness must be differentiated from seizures in neonates, because of the following features:

- Jitteriness is not associated with ocular deviation
- It is stimulus sensitive (eg, easily stopped with passive movement of the limb)
- The movement resembles a tremor, and no autonomic changes are associated with it.

Etiology of newborn seizures

The most common etiology of neonatal seizures is perinatal hypoxia-ischemia. With hypoxic-ischemic encephalopathy (HIE), the seizures usually begin within the first 24 hours after birth and are associated with obtundation. Seizures may be seen in both term and preterm infants and may include subtle, clonic, or generalized seizures. Other common etiologies include intracranial infections and intracranial hemorrhage. Intracranial hemorrhage occurs more frequently in premature than in term infants, and is estimated to account for approximately 10% of all neonatal seizures (4, 6, 7). Metabolic disturbances can also cause neonatal seizures. The most common metabolic etiologies for neonatal seizures include hypoglycemia, hypocalcemia, and hypomagnesaemia (8). Hyponatremia and hypernatremia, although less common, can also produce seizures in the neonatal period. Less frequent metabolic disorders, such as inborn errors of metabolism, are seen more commonly in infants aged over 72 hours. They may be seen after the infant starts feeding; if there is no evidence of HIE, sepsis, or hemorrhage, metabolic diseases must then be considered. Metabolic disorders that can result in neonatal seizures include aminoacidopathies, urea cycle disorders, biotinidase deficiency, mitochondrial disorders, defects in beta-oxidation, glucose transporter deficiency, and peroxisomal disorders. Pyridoxine dependency, a defect in pyridoxine metabolism, although a rare disorder, produces severe seizures in the neonatal period that are resistant to antiepileptic drug therapy (9-12). In the neonatal period, most cerebral malformation can present with seizures. Familial neonatal convulsions usually begin on the second or third day of life and can be either partial or generalized (13,14). The seizures disappear by the age of 2-6 months. A family history of seizures is common. Development is typically normal in these infants; seizures are associated with behavioral arrest, eye deviation to one side, and tonic stiffening, sometimes myoclonic jerks.

Benign sleep myoclonus is a condition, occurring only during sleep, in which rhythmic movements mimic seizures. Video EEG monitoring shows no electrographic seizures. Benign idiopathic, neonatal seizures typically present on the fifth day of life, i.e. "fifth day fits"; they occur in full-term infants and can appear to be quite fulminant, occurring up to 15-20 times per day; infants

otherwise appear healthy. The seizures are usually clonic and are sometimes associated with apnea and cyanosis. Two severe, catastrophic epileptic syndromes have also been identified during the neonatal period; Ohtahara's syndrome and early myoclonic encephalopathy fit easily into the category of neonatal generalized epileptic syndromes. Both begin in the neonatal period, usually in the first 10 days after birth. Children with these encephalopathies suffer from severe neurological diseases, with developmental delays and intractable seizures (15-17).

Work up

History: Documenting the clinical history provides important clues to the likely etiology of neonatal seizures; a family history of convulsions, genetic disorders, pregnancy history (fetal distress, preeclampsia, maternal infections), delivery history (type of delivery, antecedent events, Apgar scores, resuscitation), and postnatal history (drug withdrawal, neonatal hypocalcemia, infection) should be obtained.

Physical exam: Infants with neonatal seizures are frequently lethargic between seizures and often appear ill. Findings of the neurological examination between seizures may be normal.

Lab studies:

Serum electrolytes: Serum glucose, Calcium, and Mg should be measured; the severity of the neurological symptoms is directly correlated with the duration of the metabolic disturbance.

CSF analysis: This should include tests checking for pleocytosis, protein, and glucose concentration, gram stain and culture, xanthochromia, lactic acid and pyruvate and sometimes PCR for the herpes virus. Lethargy, vomiting, temperature instability, or subtle changes in physiologic homeostasis usually identify sepsis. Any infant with these symptoms should have a sepsis work up, including blood, urine and CSF cultures. **Metabolic investigations:** Inborn errors of metabolism are relatively rare causes of seizures in the neonatal population, however, if there is no evidence of HIE, sepsis, or hemorrhage, metabolic diseases must then be considered. Metabolic investigations should include evaluations of blood lactate, pyruvate, ammonia, quantitative aminoacids, and very long-chain fatty acids, urine-quantitative organic acids and CSF cell count,

pyruvate, lactate, glucose (with simultaneous plasma glucose). Disturbances of amino acid or organic acid metabolism are often the most common inborn errors of metabolism that present with neonatal seizures. **Renal function tests:** These tests rule out post-hypoxic renal function.

Imaging studies

Cranial ultrasound: Cranial ultrasound is easily performed at the bedside; it is a valuable tool that quickly identifies intracranial hemorrhage, particularly intraventricular hemorrhage.

Cranial C.T scan: Cranial C.T scan is a much more sensitive tool than ultrasound in detecting parenchymal abnormalities; the only disadvantage is that the sick neonate must be transported to the imaging site. **MRI:** Cranial MRI is the most sensitive test in determining the etiology of neonatal seizures. A major disadvantage is that it cannot be performed quickly.

EEG: EEG plays a vital role in properly identifying and differentiating neonatal seizures from non epileptic seizures. Surface video EEG monitoring has also demonstrated that many electrographic seizures in the newborn are not accompanied by any observable clinical phenomena and are probably underestimated.

Treatment:

The single most important factor in determining treatment of neonatal seizures is identification of the underlying etiology for the seizures. Acute neonatal seizures should be treated aggressively. When clinical seizures are present, a work up to determine an underlying etiologic cause should be initiated quickly. Treatment of neonatal seizures begins with the understanding that both seizures and their subsequent therapy may be associated with changes in respiration, heart rate, and blood pressure. Thus, to manage these changes, therapeutic strategies must be developed that ensure an adequate airway and access to circulatory system early in the course of treatment. Etiologic therapy such as treatment of hypoglycemia, hypocalcemia, and hypomagnesemia and CNS infections is critical since it may prevent further brain injury. Furthermore, these seizures may not be effectively controlled with antiepileptic drugs (AED) unless their underlying cause is treated. **Hypoglycemia:** Hypoglycemia should be corrected immediately with a 10 percent glucose solution given

intravenously at 2 ml/kg. Maintenance glucose infusion can be given to a maximum of 8mg/kg per minute. It is imperative to avoid hyperglycemia.

Hypocalcemia: Hypocalcemia associated with severe neuromuscular irritability or seizures is treated with 10 percent calcium- gluconate (100mg/kg or 1ml/kg IV). The solution is infused over 5-10 minutes, while heart rate and infusion site are closely being monitored. The dose can be repeated in 10 minutes if no response occurs.

Hypomagnesemia: Neonatal hypomagnesemia is often associated with hypocalcemia, although it can occur alone. The treatment is 50 percent solution of magnesium sulfate injected intra-muscularly at 50 mg/kg. The same dose can be repeated every 12 hours until normomagnesemia is achieved.

Pyridoxin dependency: Pyridoxin (100 mg IV) is often used empirically during EEG monitoring in infants with refractory seizures, and can have a dramatically beneficial effect on those with pyridoxine dependency.

Antiepileptic therapy

After initial management of airway and cardiovascular support, and the identification and institution of etiologic-specific therapy, the physician must decide whether to initiate antiepileptic drug (AED) therapy and which AED to use.

Phenobarbital: Phenobarbital is given as a loading dose of 20 mg/kg intravenously within 10 to 15 minutes. It can also be given intramuscularly in case there is no venous access. If there is no response within 15 minutes, 5mg /kg Phenobarbital can be given every 5 minutes until seizure activity ceases completely or until a total loading dose of 40mg/kg is given. If the seizure is controlled, then we put the patient on the maintenance dose of 3-5 mg/kg, given orally, intravenously or intramuscularly in two divided doses. In infants with hypoxic-ischemic encephalopathy, the total loading dose should not be more than 20 mg/kg since they have poor hepatic metabolism of the medication and high doses may cause toxicity in these infants.

Phenytoin: If there is no response to the loading dose of Phenobarbital, phenytoin in a loading dose of 20 mg/kg can be given intravenously within 15-20 minutes. The maintenance dose of this drug is 3-5 mg/kg given orally or intravenously. Since this drug is precipitated in dextrose water, we should wash the I.V line with normal saline

before giving this medication. Obtaining the serum drug levels of both Phenobarbital and phenytoin is recommended.

Other AEDs:

Lorazepam: Given intravenously 0.05-0.1 mg /kg

Diazepam: Given intravenously 0.1-0.3 mg /kg within 5 minutes or 0.2- 0.8 mg /kg/hr as continuous IV Infusion.

Midazolam: Given intravenously 0.03-0.1 mg/kg stat, then 0.05 mg /kg/hr as continuous IV infusion.

Duration of AED therapy:

* In most cases if the infant is receiving both phenobarbital and phenytoin, the latter can be discontinued before hospital discharge.

* If the seizure is the result of a Transient problem such as hypoglycemia or hypocalcaemia, the anticonvulsion drug can be stopped before discharge.

* In the case of normal neurological status of the infant, medication can be stopped during the neonatal period.

* If the neurological exam is abnormal, we should continue the medication until the electroencephalogram, imaging studies (MRI, brain C T scan, sonography) and neurodevelopmental assessment are normal which may be up to two to three and sometimes up to twelve months after discharge.

Prognosis and outcome of neonatal seizures:

Prognosis is determined by etiology of neonatal seizures. The EEG is also important in determining the outcome. If the seizure is due to a transient condition such as hypocalcemia,... the prognosis is good. If EEG background is normal, the prognosis is excellent for seizures to resolve. Severe EEG background abnormalities indicate poor prognosis, since such patients frequently have epilepsy.

Acknowledgments

The author would like to thank Dr. M. Imani, for his invaluable assistance in preparing the manuscript.

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