Neonatal Seizures

DEFINITION: A seizure is a paroxysmal behavior caused by hypersynchronous discharge of a group of neurons. Neonatal seizures are the most common overt manifestation of neurological dysfunction in the newborn.

BACKGROUND & PATHOGENESIS: Seizures are usually related to significant illness, occasionally requiring specific therapy. Seizures may interfere with cardiorespiratory function and with nutrition and may have detrimental long-term effects on cerebral development. Potential mechanisms of brain injury with repeated neonatal seizures include:

- Hypoventilation/apnea causing hypoxia (leading to cardiovascular collapse, diminished cerebral blood flow [CBF] and increased risk of hypoxic ischemic injury), or hypercarbia (leading to a rise in CBF and increased risk of intracranial hemorrhage (ICH).
- Elevated blood pressure increases CBF and risk of ICH.
- Increased glycolysis leading to hypoglycemia which exacerbates seizure induced brain injury.
- Excitatory amino acids (increased release) resulting in excitotoxic brain injury.

Most of these can be prevented with good intensive care and control of the seizures.

DIAGNOSIS:

Seizure type	*Occurs in*	*Clinical signs*
Subtle	Preterm and Term	Eye deviation (Term) Blinking, fixed stare (Preterm) Repetitive mouth & tongue movements Apnea Pedaling, tonic posturing of limbs
Tonic	Primarily Preterm	May be focal or generalized Tonic extension or flexion of limbs (often signals severe ICH in preterm infants)
Clonic	Primarily term	May be focal or multifocal Clonic limb movements (synchronous or asynchronous, localized or often with no anatomic order to progression) Consciousness may be preserved Often signals focal cerebral injury.
Myoclonic	Rare	Focal, Multifocal, or Generalized Lightning-like jerks of extremities (upper>lower)

Differentiation of Seizures from Nonconvulsive Movements:

- Jitteriness is distinguished clinically from clonic seizures by (1) no associated ocular movements or autonomic phenomena, (2) stimulus sensitivity, (3) tremor that is suppressed by flexing the limb.
- Distinguish benign neonatal sleep myoclonus (occurs in healthy newborns) from myoclonic seizures.

-Simultaneous monitoring with electroencephalography (EEG) and video display in newborns with subtle seizures and generalized tonic seizures has not shown consistent electrographical discharges. Some of these movements may be brainstem release phenomena rather than "epileptic seizures".

MAJOR CAUSES OF NEONATAL SEIZURES: Several causes often coexist!

Cause	***Usual Age at Onset***	***Preterm***	***Term***
Hypoxic-ischemic encephalopathy	<3 days	+++	+++
Metabolic			
Hypoglycemia	<2 days	+	+
Hypocalcemia			
Early-onset	2–3 days	+	+
Late-onset	>7 days	+	
Hypomagnesemia (often with Hypocalcemia)			
Hyper/Hyponatremia			
Drug Withdrawal	<3 days	+	+
Local Anesthetic Toxicity			
Pyridoxine (Vitamin B6) Dependency			
Disorders of Small Molecules (Amino Acid, Organic Acid &Urea Cycle Disorders)			
Disorders of Subcellular Organelles (Mitochondrial & Peroxisomal Disorders)			
Intracranial infection	<3 days	++	++
Bacterial meningitis (E. coli, Group B Strep, Listeria)			
Viral Encephalitis (Herpes Simplex, Enterovirus)			
Intrauterine Infection (CMV, Toxoplasm., HIV, Rubella, Syphilis)	>3 days	++	++
Cerebral Vascular			
Intraventricular hemorrhage	<3 days	++	
Primary subarachnoid bleed	<1 day		++
Subdural/epidural hematoma			
Focal Ischemic Necrosis (Stroke)	Variable		++
Sinus Thrombosis	Variable		+
Developmental defects	Variable	++	++
Neurocutaneous Disorders (Tuberous Sclerosis Complex, Incontinentia Pigmenti)			
Epilepsy Syndromes			
Epileptic Encephalopathies (Early Myoclonic Encephalopathy, Early Infantile Epileptic Encephalopathy)			
Benign Familial Neonatal Convulsions			

(Relative Frequency: +++ = most common; ++ = less common; + = least common. If no +, then uncommon.)

ELECTROENCEPHALOGRAPHY (EEG) is essential in diagnosis and management of neonatal seizures. As there may not be ictal activity on EEG even during a seizure (*electro-clinical dissociation*), serial EEGs or continuous EEG monitoring (when available) are of benefit. The EEG is analyzed for ictal activity (focal or multifocal spikes or sharp waves and focal monorhythmic discharges) and for background activity. Background abnormalities are predictive of (1) risk of electrographic seizures and (2) prognosis.

NEUROIMAGING: Imaging the brain is essential in determining the etiology of neonatal seizures. In the acute setting, after control of the seizures (see below), MRI scanning is very effective for determining the presence and extent of hypoxic-ischemic injury and of parenchymal brain injury. If MRI scanning is not possible acutely, CT scan is effective for determining the presence of hemorrhage and calcification (*e.g.*, congenital infection, cortical dysplasia). A more detailed look at the brain with MRI can often be done after the acute period. Unfortunately, ultrasound is not an adequate study for the diagnosis of neonatal seizures as it is not effective at detecting subdural or epidural bleeds or identifying parenchymal injury.

MANAGEMENT: Neonatal seizures require urgent treatment to **prevent brain injury**. Give anticonvulsant medication **only after adequate ventilation and perfusion have been established and the blood glucose concentration has been measured**. Seizures with hypoglycemia or hypoxia are detrimental to the brain!

1. Ensure adequate ventilation and perfusion.

2. Correct metabolic disturbances.

Hypoglycemia: (10% glucose in water) 2 mL/kg IV (0.2 g/kg) as bolus. Follow with continuous infusion at up to 8 mg/kg/min IV (see section on Hypoglycemia, P. 153).

Hypocalcemia: (calcium gluconate 10%) 100mg/kg IV over 1 to 3 minutes (**Note**: Monitor cardiac rhythm for bradycardia) Follow with maintenance of 500 mg/kg/24 hrs IV or PO

Hypomagnesemia: (magnesium sulfate) 25-250 mg/kg/dose IV/IM

3**. Begin anticonvulsant therapy.**

Phenobarbital: 20 mg/kg IV. If necessary, additional 10-20 mg/kg IV in 10 mg/kg aliquots (**Note**: monitor blood pressure and respiration) Maintenance: 4–6 mg/kg/24 hrs IV/PO
If 40 mg/kg of Phenobarbital is not effective, proceed to Lorazepam and obtain consult with the Neurology Service for advice regarding seizure treatment. (While the literature supports the use of Phenytoin as a second line agent, our experience is that Lorazepam is more effective in the acute setting.)

Before giving second dose or second medication ask yourself: (1) Do I have the correct diagnosis? (2) Are ventilation and perfusion optimal? (3) Have I recognized and corrected any metabolic disturbance?

Lorazepam: 0.05 mg/kg to 0.10 mg/kg IV in 0.05 mg/kg increments over several minutes. (**Note**: Monitor closely for respiratory depression.) The half-life in asphyxiated newborns is ~40 hours; duration of action 6-24 hours!

Phenytoin: 20 mg/kg IV (diluted in 0.9% NaCl) (Maximal rate: 1 mg/kg/min. Monitor cardiac rate and rhythm). Maintenance 5–10 mg/kg/24h IV (Phenytoin is VERY poorly absorbed PO in the newborn).

Fourth line anticonvulsants include Paraldehyde. If you must proceed to this stage, then Neurology should have been consulted for guidance with dosage and other management issues.

Pyridoxine deficiency is a rare cause of neonatal seizures and should be considered in any newborn with intractable seizures. The diagnosis is made by pyridoxine IV with concurrent EEG.

OUTCOME AND DURATION OF TREATMENT: The outcome following neonatal seizures depends primarily on the underlying cause. The presence of both clinical and electrographic seizures in the newborn often indicates some degree of brain injury and may alter the prognosis of the underlying disorder (*e.g.*, hypoxic-ischemic injury).

The duration of treatment following neonatal seizures is also determined by the underlying cause (*i.e.,* related to risk of recurrence), the physical examination and the EEG. The following guidelines aim to continue Phenobarbital for the briefest time possible:

- -When seizures have stopped and if the neurological examination is normal, consider stopping Phenobarbital.
- -If the neurological examination remains abnormal, then consider stopping medication if the EEG is normal.
- -Make this evaluation prior to discharge and then frequently after discharge, if the child has been discharged on Phenobarbital.
- -Stop Phenytoin when IV therapy is stopped as this drug is *very* difficult to maintain PO.