Seizures in the Newborn

Abstract

Seizures in the newborn period constitute a medical emergency. Subtle seizures are mild paroxysmal alterations in motor or autonomic activity and are unique to the neonatal period. They are likely to be missed or confused with benign movements observed commonly in preterm children. Focal clonic seizures have a better prognosis as compared to myoclonic seizures for long term neuro-developmental outcome. Hypoglycemia and hypocalcemia are common causes and should be excluded in all neonates with seizures. Seizures due to sub-arachnoid hemorrhage and late onset hypocalcemia carry a better prognosis as compared to seizures due to hypoglycemia, meningitis and cerebral malformations. Multiple etiologies can co-exist in neonatal seizures and a comprehensive approach for management of neonatal seizures has been described.

Key words: Seizures, electro-encephalo-graph (EEG)
A seizure in the neonatal period is an emergency that reflects potentially significant insults to the immature brain. Diagnostic and therapeutic interventions should thus be established promptly.

1. Definition
A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e. motor, behavior and/or autonomic function. This definition includes:

1. Epileptic seizures: phenomena associated with corresponding EEG seizure activity e.g. clonic seizures
2. Non-epileptic seizures: clinical seizures without corresponding EEG correlate e.g. subtle and generalized tonic seizures
3. EEG seizures: Abnormal EEG activity with no clinical correlation.

2. Incidence
National collaborative perinatal project reported an incidence of 5/1000 per 1000 live births between 1959 and 1966. The National Neonatal-Perinatal Database (NNPD) of India that collated information from 18 centers from across the country in the year 2002-03 had reported an incidence of 1.0%.

3. Classification
Four types of seizures have been identified. (See Table 1)

3.1 Subtle seizures: They are called subtle because the clinical manifestations are often mild and frequently missed. Subtle seizures are usually mild paroxysmal alterations in
motor, behavior or autonomic function that are not clearly clonic, tonic or myoclonic. They are the commonest type and constitute 50% of all seizures. Common examples of subtle seizures include:

1. **Ocular**: Tonic horizontal deviation of eyes or sustained eye opening with ocular fixation or cycled fluttering

2. **Oral–facial–lingual movements** (chewing, tongue-thrusting, lip-smacking)

3. **Limb movements** (cycling, paddling, boxing-jabs)

4. **Autonomic phenomena** (tachycardia or bradycardia)

5. **Apnea** may be a rare manifestation of seizures. Apnea due to seizure activity has an accelerated or a normal heart rate when evaluated 20 seconds after onset. Bradycardia is thus not an early manifestation in convulsive apnea but may occur later due to prolonged hypoxemia.

3.2 **Clonic seizures**: They are rhythmic movements of muscle groups. They have a fast and a slow component and occur with a frequency of 1-3 jerks per second. They are most commonly associated with abnormal EEG changes.

3.3 **Tonic seizures**: This type refers to a sustained flexion or extension of axial or appendicular muscle groups. These seizures may be focal or generalized and may resemble decerebrate (tonic extension of all limbs) or decorticate posturing (flexion of upper limbs and extension of lower limbs). Usually there are no EEG changes in generalized tonic seizures.

3.4 **Myoclonic seizures**: These manifest as single or multiple slow lightning fast jerks of the upper or lower limbs and are usually distinguished from clonic movements because of more rapid speed of myoclonic jerks, absence of slow return and predilection for flexor
muscle groups. Common changes seen on the EEG include burst suppression pattern, focal sharp waves and hypsarrhythmia

*Myoclonic seizures carry the worst prognosis in terms of neuro-developmental outcome and seizure recurrence. Focal clonic seizures have the best prognosis.*

4. Non-epileptic movements commonly confused with seizures:

4.1 *Jitteriness or tremors:* Features characteristic of tremors include fast movements (4-6 per sec), absence of a fast and slow component, provocation by stimulation of the infant or stretching a joint, termination by passive flexion of the limb and absence of associated eye movements, autonomic changes and EEG correlates.

4.2 *Normal movements seen more commonly in preterms*

- Benign neonatal sleep myoclonus: Occur during nonREM sleep in preterms in the first week of life, restraint and benzodiazepines may increase the jerks, rapidly abolished on arousal normal EEG
- Fragmentary myoclonic jerks
- Eye movements: Roving or dys-conjugate eye movements with occasional non-sustained nystagmoid jerks.

5. Causes of neonatal seizures

5.1 *Hypoxic-ischemic encephalopathy (HIE):* HIE secondary to perinatal asphyxia is the commonest cause of seizure in neonates, constituting 50-65% of all seizures. Most seizures (50-65%) due to HIE start within 12 hrs, remaining have an onset within 24-48 hours. Additional problems like hypoglycemia, hypocalcemia and intracranial hemorrhage may co-exist in neonates with perinatal asphyxia and these should be
excluded in a setting of HIE. Subtle seizures are the most common type of seizures following HIE.

5.2 Intracranial hemorrhage:
Seizures due to sub-arachnoid, intra-parenchymal or subdural hemorrhage occur more often in term babies and seizures related to intraventricular hemorrhage (IVH) occur in preterms. Most seizures due to intracranial hemorrhage occur between 2-7 days. Seizures occurring in a well term baby on day 2-3 of life may be due to sub-arachnoid hemorrhage

5.3 Metabolic causes:
Common metabolic causes of seizures include hypoglycemia, hypocalcemia, hypomagnesemia and rarely pyridoxine deficiency and inborn errors of metabolism

5.4 Infections:
Meningitis should be excluded in all neonates with seizures. Meningo-encephalitis secondary to intrauterine infections (TORCH group, syphilis) may present as seizures in the neonatal period.

5.5 Developmental defects:
Cerebral dysgenesis and neuronal migration disorders are rare causes of seizures in the neonatal period.

5.6 Miscellaneous:
These causes include polycythemia, maternal narcotic withdrawal, drug toxicity (e.g. theophylline, doxapram), local anesthetic injection into scalp and phacomatosis (e.g. tuberous sclerosis, incontinentia pigmentii). Accidental injection of local anesthetic into scalp may be suspected in the presence of unilateral fixed and dilated pupil. Multifocal
clonic seizures on the 5th day may be related to low zinc levels in the CSF fluid (benign idiopathic neonatal convulsions).

Seizures due to SAH and late onset hypocalcemia carry a good prognosis for long term neuro-developmental outcome while seizures related to hypoglycemia, cerebral malformations and meningitis have a high risk for adverse outcome.

6. Diagnosis/Approach

6.1 Seizure history:
A complete description of the seizure should be obtained from the attendant. History of associated eye movements, restraint of episode by passive flexion of the affected limb, associated change in color of skin (mottling or cyanosis), any associated autonomic phenomena and whether conscious/ sleeping at the time of seizure should be elicited. The day of life on which the seizure occurred may provide an important clue to its diagnosis. Seizures occurring on day 0-3 may be related to perinatal asphyxia, intracranial hemorrhage, metabolic and developmental defects. Seizures occurring on day 4-7 may be due to sepsis, meningitis, metabolic causes and developmental defects.

6.2 Antenatal history:
History suggestive of intra-uterine infection, maternal diabetes and narcotic addiction should be elicited in the antenatal history. A history of sudden increase in fetal movements may be suggestive of intra-uterine convulsions.

6.3 Perinatal history:
Perinatal asphyxia is the commonest cause of neonatal seizures and a detailed history including history of fetal distress, decreased fetal movements, instrumental delivery, need
for resuscitation in labor room, low Apgar scores (<3 at 1 and/ or 5 minutes) and abnormal cord pH (≤7) and base deficit (≤-10) should be obtained. Use of a pudendal block for mid-cavity forceps may be associated with accidental injection of the local anesthetic into the fetal scalp.

6.4 Feeding history:
Appearance of clinical features including lethargy, poor activity, drowsiness, and vomiting after initiation of breast-feeding may be suggestive of inborn errors of metabolism. Late onset hypocalcemia should be considered in the presence of top feeding with cows’ milk.

6.5 Family history:
History of consanguinity in parents, family history of seizures or mental retardation and early fetal/neonatal deaths would be suggestive of inborn errors of metabolism. History of seizures in either parent or sib/s in newborn period may suggest BFNC.

7. Examination

7.1 Vital signs: Heart rate, respiration, blood pressure, capillary refill time and temperature should be recorded.

7.2 General examination:
Gestation, birth-weight and weight for age should be recorded as it may provide important clues to the etiology of the seizure. Seizures in a well term baby may be suggestive of sub-arachnoid hemorrhage. Seizures in a large for date baby may be due to hypoglycemia. The neonate should be examined for the presence of any obvious malformation or dysmorphic features.
7.3 **CNS examination**

Presence of a bulging anterior fontanelle may be suggestive of meningitis or intracranial hemorrhage. A detailed neurological examination should include assessment of consciousness (alert/drowsy/comatose), tone (hypotonia or hypertonia) and fundus examination for chorioretinitis.

7.4 **Systemic examination**

Presence of hepato-splenomegaly or an abnormal urine odor may be suggestive of inborn errors of metabolism. The skin should be examined for the presence of any neurocutaneous markers. Presence of hypopigmented macules/ Ashleaf spot would be suggestive of tuberous sclerosis.

8. **Investigations**

8.1 **Mandatory investigations:**

Investigations that should be considered in all neonates with seizures include blood sugar, hematocrit, bilirubin (if jaundice is present clinically), serum electrolytes (Na, Ca, Mg) arterial blood gas, anion gap, cerebrospinal fluid (CSF) examination, ultrasound (US) head and electroencephalography (EEG). ABG not easily accessible, may help for IEM which is not a very common cause of neonatal seizures. CSF examination should be done in all cases as seizures may be the first sign of meningitis. It should not be omitted even if another etiology (e.g. hypoglycemia) is present, because meningitis can coexist. CSF study may be withheld temporarily if severe cardio respiratory compromise is present or in cases with severe birth asphyxia (documented poor cord pH, seizure onset within 12-24 hrs).

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One should carry out all these investigations even if one or more investigations are positive, as multiple etiologies may coexist, e.g. sepsis, meningitis and hypoglycemia.

8.2 Specific investigations:

These may be considered in neonates who do not respond to a combination of phenobarbitone and phenytoin or earlier in neonates with specific features. These include neuroimaging (CT, MRI), screen for congenital infections (TORCH) and for inborn errors of metabolism.

8.3 Imaging

Neurosonography is an excellent tool for detection of intraventricular and parenchymal hemorrhage but is unable to detect SAH and sub-dural hemorrhage. It should be done in all infants with seizures. A CT scan should be done in all term infants where an etiology is not available after the first line of investigations. It can be diagnostic in sub-arachnoid hemorrhage and developmental malformations. A MRI scan is indicated only if investigations do not reveal any etiology and seizures are resistant to usual anti-epileptic therapy. It can be diagnostic in cerebral dysgenesis, lissencephaly and other neuronal migration disorders.

8.4 Screen for congenital infections

A TORCH screen and VDRL should be considered in the presence of hepatosplenomegaly, thrombocytopenia, growth retardation, small for gestational age and presence of chorioretinitis.
8.5 Metabolic screen

A metabolic screen includes blood and urine ketones, urine reducing substances, blood ammonia, anion gap, urine and plasma aminoacidogram, serum and CSF lactate/ pyruvate ratio.

8.6 Electro-encephalogram (EEG)

EEG has both diagnostic and prognostic role in seizures. It should be done in all neonates needing anti-convulsant therapy. Ictal EEG may be useful for the diagnosis of suspected seizures and for diagnosis of seizures in muscle-relaxed infants. It should be done as soon as the neonate is stable enough to be transported for EEG, preferably within first week. EEG should be performed for at least 1 hour\(^8\). Inter-ictal EEG is useful for long-term prognosis of neonates with seizures. A background abnormality in both term and preterm neonates indicates a high risk for neurological sequelae. These EEG changes include burst-suppression pattern, low voltage invariant pattern and electro-cerebral inactivity.

9. Treatment

9.1 Initial medical management:

The first step in successful management of seizure is to nurse the baby in thermoneutral environment and ensure airway, breathing and circulation (TABC). \(\text{O}_2\) should be started, IV access should be secured, and blood should be collected for sugar and other investigations. During all this, a brief relevant history and quick clinical examination should be done (\textit{vide supra}). All this should not require more than 2-5 minutes.

9.2 Hypoglycemia:
If glucostix shows hypoglycemia or if there is no facility to test blood sugar immediately, 2 ml/kg of 10% dextrose should be given by bolus followed by a maintenance infusion of 6-8 mg/kg/min.

9.3 Hypocalcemia:
If hypoglycemia has been treated or excluded as a cause of convulsions, the neonate should receive 2ml/kg of 10% calcium gluconate IV over 10 minutes under strict cardiac monitoring. If ionized calcium levels are suggestive of hypocalcemia, the newborn should receive calcium gluconate at 8 ml/kg/d for 3 days. If seizures continue despite normal calcium magnesium 0.25 ml/kg of 50% should be given i.m.

9.4 Anti-epileptic drug therapy (AED)
Anti-epileptic drugs (AED) should be considered in the presence of even a single clinical seizure since clinical observations tend to grossly underestimate electrical seizures (diagnosed by EEG), and facilities for continuous EEG monitoring are usually not available. AED should be given if seizures persist even after correction of hypoglycemia/hypocalcemia.

10. Pharmacotherapy for neonatal seizures
10.1. Phenobarbitone(Pb)
It is the drug of choice. The dose is 20 mg/kg/IV slowly over 20 minutes (not faster than 1 mg/kg/min). If seizures persist after completion of this loading dose, repeat dose of phenobarbitone 10 mg/kg may be used every 20-30 minutes till a total dose of 40 mg/kg has been given. The maintenance dose is 3-5 mg/kg/day in 1-2 divided doses, started 12 hours after the loading dose.

10.1.a Prophylactic phenobarbitone in asphyxia
Some interest has been generated in the protective role of prophylactic phenobarbitone in newborns with perinatal asphyxia. A dose of 40 mg/kg administered prophylactically was associated with a better neuro-developmental outcome at 3 years of age. However another study using 10 mg/kg in a similar fashion has reported an immediate adverse outcome with the use of phenobarbitone. Recommendation for use of prophylactic phenobarbitone still awaits further studies.

10.2 Phenytoin (PHT)
Phenytoin is indicated if the maximal dose of phenobarbitone (40 mg/kg) fails to resolve seizures or earlier, if adverse effects like respiratory depression, hypotension or bradycardia ensue with phenobarbitone. The dose is 20 mg/kg IV at a rate of not more than 1 mg/kg/min under cardiac monitoring. It should not be made in dextrose as it precipitates in it. A repeat dose of 10 mg/kg may be tried in refractory seizures. The maintenance dose is 3-5 mg/kg/d (maximum of 8 mg/kg/d) in 2-4 divided doses. Oral suspension has very erratic absorption from gut in neonates, so it should be avoided. Thus only IV route is preferred in neonates and it should preferably be discontinued before discharge.

Fosphenytoin, the prodrug of phenytoin, does not cause the same degree of hypotension or cardiac abnormalities, has high water solubility (therefore can be given IM), and is less likely to lead to soft-tissue injury compared with phenytoin. It is dosed in phenytoin equivalents (1.5 mg/kg of fosphenytoin is equivalent to 1 mg/kg of phenytoin).

10.3 Benzodiazepines
This group of drugs may be required in 15% of newborns with seizures that do not respond to phenobarbitone and phenytoin. Benzodiazepines available are Diazepam,
Lorazepam, Midazolam and Clonazepam. Diazepam is generally avoided due to its short duration of action, narrow therapeutic index, and because of the presence of sodium benzoate as a preservative in diazepam formulations. Lorazepam is preferred over diazepam as it has a longer duration of action and less sedation and cardiovascular adverse effects. Midazolam is faster acting than lorazepam and may be administered as an infusion. It requires strict monitoring for respiratory depression, apnea and bradycardia. The doses of these drugs are given below:

- **Diazepam**: 0.25 mg/kg IV bolus (0.5 mg/kg rectal); may be repeated 1-2 times.
- **Lorazepam**: 0.05 mg/kg IV bolus over 2-5 minutes; may be repeated
- **Midazolam**: 0.15 mg/kg IV bolus followed by infusion of 0.1 to 0.4 mg/kg/hour.
- **Clonazepam**: 0.1–0.2 mg/kg IV bolus followed by infusion 10-30 µg/kg/hr.

_Equipment for resuscitation and assisted ventilation should be available at the bedside of all neonates given multiple doses of AED._

According to Volpe, the expected response to anticonvulsants is 40% to the initial 20-mg/kg loading dose of phenobarbitone, 70% to a total of 40 mg/kg of PB, 85% to a 20-mg/kg LD of PHT, and 95% to 100% to 0.05 to 0.10 mg/kg lorazepam\(^4\). In exceptional circumstances when the seizures are refractory to these first-line drugs, the following second-line drugs might be tried.

**10.4 Antiepileptic drugs for seizures refractory to above treatment**

**Lidocaine**: Start with 4mg/kg/hr IV on first day, reduce by 1mg/kg/hr on each subsequent day or load with 2mg/kg IV and maintain on 6 mg/kg/hr. Adverse effects include arrhythmias, hypotension and seizures. It should not be administered with phenytoin.
**Paraldehyde**: It may be used in seizures refractory to the first line drugs. A dose of 0.1-0.2 ml/kg/dose may be given IM or 0.3 ml/kg/dose mixed with coconut oil in 3:1 may be used by per rectal route. Additional doses may be used after 30 minutes and q 4-6 hourly. Adverse effects include pulmonary hemorrhage, pulmonary edema, hypotension, and liver injury.

**Sodium valproate**: It can be used for maintenance therapy in neonates. Per rectal route may be used in acute condition. IV preparation is now available. Dose is 20-25 mg/kg/d followed by 5-10 mg/kg every 12 hours.

**Vigabatrin**: It has been used in neonates for refractory seizures, primarily for infantile spasms. The dose is 50 mg/kg/day.

**Topiramate**: It shows promise in neonatal seizures because of its potential neuroprotective effect against injury caused by seizures. Topiramate has been used for refractory infantile spasms in infants. The higher volume of distribution compared with other drugs requires higher initial and maintenance doses of approximately 3 mg/kg.

### 10.5 Other therapies

**Pyridoxine**: Therapeutic trial of pyridoxine is reserved as a last resort. IV preparation is not available in India and an IM preparation may be used instead. (1 ml of neurobion has 50-mg pyridoxine and 1 ml each may be administered in either the gluteal region or anterolateral aspect of thigh). This should be done in the NICU as hypotension and apnea can occur. If preparation available IV route is preferable.

**Exchange transfusion**: is indicated in life-threatening metabolic disorders, accidental injection of local anaesthetic, trans-placental transfer of maternal drugs (e.g. chlorpropamide) and bilirubin encephalopathy.
10.6 Maintenance anti-epileptic therapy

Principles of AED used in older children and adults are applicable to neonates also. Monotherapy is most appropriate in attempts to control seizures. Attempts should be made to stop all anti-epileptic drugs and wean the baby to only phenobarbitone at 3-5 mg/kg/day. If seizures are uncontrolled or if clinical toxicity appears a second AED may be added. The choice of the second drug may vary from phenytoin, carbamezepine and valproic acid.

10.7 When to discontinue AED

This is highly individualized and no specific guidelines are available. We follow an adaptation of the protocol recommended by JJ Volpe. We usually try to discontinue all medication at discharge if clinical examination is normal, irrespective of etiology and EEG. If neurological examination is persistently abnormal at discharge, AED is continued and the baby is reassessed at 1 month.

If the baby is normal on examination and seizure free at 1 month, phenobarbitone is discontinued over 2 weeks. If neurological assessment is not normal, an EEG is obtained. If EEG is not overtly paroxysmal, AED are tapered and stopped. If EEG is overtly abnormal, the infant is reassessed in the same manner at 3 months and then 3 monthly till 1 year of age.
References


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### Table 1. Types of seizures

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Occurs in</th>
<th>Clinical signs</th>
<th>EEG changes</th>
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<tbody>
<tr>
<td>Subtle</td>
<td>Preterm and Term</td>
<td>Eye deviation (Term)               Blinking, fixed stare (Preterm)  Repetitive mouth &amp; tongue movements  Apnea Pedaling, tonic posturing of limbs</td>
<td>Usually No</td>
</tr>
<tr>
<td>Tonic</td>
<td>Primarily Preterm</td>
<td>May be focal or generalized       Tonic extension or flexion of limbs (often signals severe ICH in preterm infants)</td>
<td>Usually No</td>
</tr>
<tr>
<td>Clonic</td>
<td>Primarily term</td>
<td>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.</td>
<td>Yes</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Rare</td>
<td>Focal, Multifocal, or Generalized Lightning-like jerks of extremities (upper&gt;lower)</td>
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Flow diagram of neonate with seizures

Neonate with seizures:
- Identify and characterize the seizure
- Secure airway, and optimize breathing, circulation and temperature
- Start O₂ if seizures are continuous
- Secure IV access and take samples for baseline investigations including sugar, calcium, magnesium, sodium, potassium, arterial blood gas, hematocrit, sepsis screen
- If hypoglycemic (blood sugar<40 mg/dl): 2ml/kg of 10% dextrose should be given immediately. (For further management see hypoglycemia protocol).
- If blood sugar is in normal range, sample for ionized calcium should be withdrawn and 2 ml/kg of calcium gluconate (10%) should be given IV under cardiac monitoring
- Brief history and quick clinical examination
- If seizures persist, start **phenobarbitone 20mg/kg stat over 20 minutes.**

Seizures continue

- Repeat phenobarbitone 10 mg/kg/dose till a total of 40 mg/kg
  - Seizures continue
  - Start phenytoin 20 mg/kg/dose
  - Seizures continue
  - Repeat phenytoin 10 mg/kg/dose

Seizures stop (-)

- CSF study
- US head, EEG

Seizures continue

- Consider Lorazepam / midazolam bolus and midazolam infusion if needed
- Consider ventilation
  - CSF study, CT / MRI, EEG
  - Metabolic work up for IEM
  - TORCH screen if indicated

Seizures controlled

- Wean AED slowly to maintenance phenobarbitone
Flow diagram on weaning and duration of anticonvulsant therapy

Newborn on anticonvulsant therapy

Wean all antiepileptic drugs except phenobarbitone once seizure controlled

Perform neurological examination prior to discharge

Normal

Stop phenobarbitone prior to discharge

Abnormal

continue phenobarbitone for 1 month

Repeat neurological examination at 1 month

Normal examination at 1 month

Evaluate EEG

Taper drugs over 2 weeks

Normal EEG

Taper drugs over 2 weeks

Abnormal EEG

Continue drug; reassess at 3 months of age
Intractable seizures may need lifelong therapy; consider switching over to other drugs (phenytoin or carbamazepine)