Seizures in Newborn: An Update

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Abstract
Neonatal seizure is the most prominent neurological dysfunction in the neonatal period which constitutes a medical emergency. Seizures result from excessive depolarization of neurons within the nervous system. Tonic, clonic, subtle and myoclonic are the different forms of neonatal seizure. Among the causes hypoxic ischemic encephalopathy is the commonest. Jitteriness and benign neonatal sleep myoclonus should be differentiated from the neonatal seizure. Proper history taking and meticulous examination should aimed to identify the seizure and find out the aetiology. Important investigations include blood sugar, serum electrolytes (Na, Ca, Mg), arterial blood gas, anion gap, cerebrospinal fluid examination, ultrasound examination of the head and electroencephalography. Upon identification of common metabolic derangements like hypoglycaemia, hypocalcaemia, hypomagnesaemia, they are treated as per recommended protocol. The rest of the symptomatic seizures (nonmetabolic) are treated with phenobarbitone. If seizures failed to respond or recur after Phenobarbitone therapy, Phenytoin, Midozolam are the subsequent options. As the recurrence rate is relatively small and the potential toxicities are high on developing brain, the good practice is to stop anticonvulsant as early as possible. Neonatal seizures have an adverse effect on neurodevelopmental outcome and predispose to cognitive, behavioral, or epileptic complications in later life.

Key words: Neonatal, seizure, newborn, convulsion

Introduction
A seizure is defined clinically as a paroxysmal alteration in neurological function like motor, behaviour and/or autonomic function1. The most prominent feature of neurologic dysfunction in the neonatal period is the occurrence of seizures. The prevalence of seizure is 2-3/1000 live births in term and 10-15/1000 in preterm deliveries2. Seizures in the newborn period constitute a medical emergency. Seizures represent the most distinctive signal of neurological disease in the newborn period. It is important to recognize seizures, determine their aetiology and treat them because the seizures may be related to significant diseases that require specific treatment and may lead to brain injury2.

Pathophysiology
A seizure results when there is an excessive synchronous electrical discharge like depolarization of neurons within the central nervous system3. Depolarization is produced by the inward migration of sodium and repolarization is produced by the efflux of potassium. Maintenance of potential across the membrane requires an energy (adenosine triphosphate or ATP) dependent pump which extrudes sodium and takes in potassium. Although the fundamental mechanism of neonatal seizures is generally unknown, current data suggest that the excessive depolarization may result for at least the following reasons3. First, a disturbance in energy production can result in a failure of sodium-potassium pump. Hypoxemia, ischemia and hypoglycemia can result sharp decrease in energy production. Second, a relative excess of excitatory versus inhibitory neurotransmitter can result in an excessive rate of depolarization. Under conditions of hypoxemia, ischaemia and hypoglycemia, extra cellular level of glutamate increases. Third, a deficiency of inhibitory neurotransmitter like relative excess excitatory neurotransmitter, can result in an excessive rate of depolarization. Pyridoxine dependency is accompanied by decreased brain and cerebrospinal level of gamma amino butyric acid (GABA). Fourth, calcium and magnesium interact with the neuronal membrane to cause an inhibition of sodium movement. Thus, hypocalcaemia and hypomagnesaemia would be expected to cause an increase in sodium influx and depolarization3.
Classification

According to clinical presentation and EEG changes

Seizures are:

1. Tonic: a. Focal, Common, Sustained posturing of a limb, asymmetric posturing of trunk or neck; b. Multifocal, Uncommon, Tonic extension of upper and lower limbs, mimicking decerebrate posturing or, Tonic flexion of upper and lower limbs (mimicking decorticate posturing)

2. Clonic : a. Focal, Common, Well localized clonic jerking, usually not unconscious; b. Multifocal, Common, Multifocal clonic movements; simultaneous or in sequence or non-ordered migration


Oral-buccal-lingual movements : a. chewing common in preterm babies; b. Lip smacking, cry grimace

Limb movements: a. Stepping, pedaling, rotary movements; b. Apnoeic spell common in term babies

4. Myoclonic : a. Focal, Multifocal, Common, Well localized, single or multiple, migrating jerks usually of limbs; b. Generalized, Single or several bilateral synchronous jerks or flexion movements occurring more in upper than in lower limbs

Aetiology

1. Hypoxic ischaemic encephalopathy (HIE): HIE secondary to perinatal asphyxia is the commonest cause of seizure in neonates, constituting 50-65% of all seizures. Most seizures due to HIE start within 12 hours, remaining have onset within 24-48 hours. Subtle seizures are the most common type of seizures.

2. Intracranial hemorrhages: Seizures due to subarachnoid, intra-parenchymal or subdural haemorrhages occur more often in term babies whereas seizures related to intraventricular haemorrhage (IVH) occur in preterms. Most seizures due to intracranial haemorrhage occur between 2-7 days

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

4. Metabolic causes: Common metabolic causes of seizures include hypoglycemia, hypocalcaemia, hypomagnesaemia, hyponatremia, hypernatremia (specially during correction) rarely pyridoxine deficiency, pyridoxine dependency, organic acid, amino acid and urea cycle disorders, glucose transport defects and other inborn errors of metabolism.

5. Developmental defects: Many aberrations of brain development like cerebral cortical dysgenesis and neuronal migration disorders are rare causes of seizures in the neonatal period

6. Cerebral infarcts: Both arterial and venous stroke.

7. Miscellaneous: These causes include polycythemia, maternal narcotic withdrawal, drug toxicity (e.g. theophylline), and local anaesthetic injection into scalp and neurocutaneous diseases.

8. Neonatal seizure syndrome: Several syndrome like benign familial neonatal seizure, benign idiopathic neonatal seizure (Fifth day fits), Smith-Lemli-Opitz syndrome are associated with neonatal seizure4-6

Non convulsive movements commonly confused with seizure. These are as follows :2

1. Jitteriness or Tremors: Features characteristics of jitteriness include fast movements (4-6/sec), provocation by stimulation, and termination by passive flexion of limbs, absence of associated eye movements, autonomic changes (tachycardia, apnoea, salivation and vasomotor phenomena) and EEG changes.

2. Benign neonatal sleep myoclonus: The mechanism for such nonepileptiform myoclonus is unclear but maybe related to a transient dysmaturity of the brainstem reticular-activating system. Presents in the first week of life. Always occur during sleep, rapidly abolished by arousal; never occur during wakefulness. Precipitated by gentle rhythmic rocking or tactile stimuli. Preictal, ictal and post-ictal EEG is normal. Resolves spontaneously over weeks to months. Long-term outcome is good and epilepsy does not develop later.

Approach to diagnose the neonatal surgery

History taking

1. Seizure History: A complete description of seizure should be obtained from the attendant. History of associated eye movements, associated changes in skin colour (mottling or cyanosis), any associated autonomic phenomena and whether conscious/sleeping at the time of seizure should be elicited. The day of onset of seizure 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. Seizures in a term well baby may be due to subarachnoid haemorrhage.

2. Antenatal History: History suggestive of intrauterine infection, maternal diabetes and narcotic addiction should
be taken. A history of sudden increase in foetal movements may be suggestive of intra-uterine convulsions.

3. Perinatal History: History of foetal distress, decreased foetal movements, instrument delivery, need for resuscitation in labor room, low Apgar scores (<3 at 1m) should be obtained.

4. Feeding History: Lethargy, poor activity, drowsiness and vomiting after initiation of breast feeding may be suggestive of inborn errors of metabolism.

5. Family History: History of consanguinity in parents, family history of seizures or mental retardation and early foetal/neonatal deaths would be suggestive of inborn errors of metabolism.

Examination Findings

1. General examination: Vital signs like heart rate, respiration, blood pressure, capillary refill time and temperature should be recorded. Gestational age, birth weight should be recorded as it may provide important clues to the aetiology of seizures. Seizure in a large for age baby may be due to hypoglycemia. The neonate should be examined for the presence of any obvious malformation, dysmorphic features. The skin should be examined for presence of any neurocutaneous markers. Presence of any hypopigmented macules/ Ashleaf spot would be suggestive of tuberous sclerosis.

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

3. Examination of abnormal movements: Feature that would help in differentiation of nonepileptiform from seizures include absence of associated eye movements, absence of autonomic changes, cessation of movement on holding the involved part and a normal sensorium. Details regarding the frequency and duration of abnormal movements should also be recorded.

4. Systemic examination: Presence of hepatosplenomegaly or an abnormal urine odour may be suggestive of inborn errors of metabolism.

Investigation

Investigation needs to be individualized depending upon clinical presentation, perinatal history and physical examination.

First lines of investigation are blood sugar, serum electrolytes (Na, Ca, Mg), Arterial blood gas, cerebrospinal fluid (CSF) examination (if indicated)-CSF study is very important as meningitis can coexist with another etiology and seizure may be the first sign of meningitis. But lumbar puncture may be withheld temporarily in severe cardio-respiratory compromise or in cases with severe birth asphyxia, serum bilirubin (if jaundice present), Ultrascanogram of the brain is an excellent tool for the detection of intraventricular haemorrhage and ventricular dilatation but is unable to detect subarachnoid hemorrhage and sub-dural hemorrhage, EEG has both diagnostic and prognostic role in seizures. It should be done as soon as the neonate is stable enough to transport for EEG, preferably within first week. Interictal 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. One should carry out all these investigations even if one or more investigations are positive, as multiple aetiologies may coexist, e.g. sepsis, meningitis and hypoglycemia. However, all seizures do not have abnormal EEG pattern, because of immaturity of the brain and interictal scalp recording may fail to pickup seizure activity. There is often poor correlation between electrographic and clinical manifestations of neonatal seizure. Digital continuous EEG monitoring is an essential tool to detect seizure.

Second line of investigation are a TORCH screening and VDRL test is indicated in the presence of hepatosplenomegaly, thrombocytopenia, growth retardation, small for gestational age and chorioretinitis, screening of metabolic disorders is important. Inborn errors of metabolism should be considered in the presence of seizures occurring after introduction of feed, presence of lethargy, coma, vomiting, poor feeding and family history of seizures in the sibs or foetal/sibling death. A metabolic screen include blood and urine pH, urinary reducing substances, blood ammonia, anion gap, urine and serum aminoacidogram, and serum and CSF lactate/pyruvate ratio. CT scan or MRI of brain is usually not available after the first line investigations and is diagnostic in sub-arachnoid hemorrhage. An MRI scan is usually not required and done only if investigations do not reveal any etiology and seizures are resistant to usual anti-convulsive therapy. It can be diagnostic in cerebral dysgenesis, lissencephaly and other neuronal migration disorders.

Treatment

Flow diagram of neonate with seizures (Figure 1) Identify and characterize the seizure:
- Secure airway and optimize breathing, airway, circulation and temperature
- Start Oxygen of seizures are continuous
- Secure IV access and take samples for baseline investigations including sugar, Ca, Mg
- If hypoglycemia (blood sugar <40mg/dl) present then 10% glucose in water 2 ml/kg bolus is followed by continuous infusion at up to 8 mg/kg/min.
- If seizure persist, start Phenobarbitone 20mg/kg stat over 10-15 min.
- To treat hypocalcaemia IV calcium gluconate 10% 2ml/kg over 10 minutes with cardiac rhythm monitoring and 8 ml /kg/day is given as maintenance therapy.
- Hypomagnesaemia is treated with 50% solution of magnesium in a dose of 0.2 ml/kg.

### Prognosis
The prognosis for infants with seizures in the neonatal period has improved over the past several decades. The incidence of neurological sequelae (mental retardation, motor deficit, seizures) in survivors changed and has been approximately 25-35%. The two most useful approaches in estimating outcome utilize the EEG and recognition of underlying neurological sequelae. If the EEG background is normal, the prognosis is excellent for seizures to resolve;

Figure 1: Management of neonatal seizure
normal development is likely. Severe EEG background abnormalities indicate poor prognosis; such patients frequently have cerebral palsy and epilepsy. The presence of spikes on EEG is associated with a 30% risk of developing future epilepsy. The prognosis following neonatal seizures that result from isolated subarachnoid hemorrhage is excellent, with 90% of children not having residual neurologic deficits. Clearly outcome is poorest among the smallest infants, who have the most serious life threatening illness. Pisani et al devised a scoring system for early prognostic assessment after neonatal seizures. Analysis of 106 newborns who had neonatal seizures and were followed prospectively to 24 months' of age identified 6 independent risk factors for adverse outcome like: (1) birth weight, (2) Apgar score at 1 minute, (3) neurologic examination at seizure onset, (4) cerebral ultrasonogram, (5) efficacy of anticonvulsant therapy, and (6) presence of neonatal status epilepticus. Each variable

![Flow Diagram on Weaning and Duration of Anticonvulsant Therapy](image)

**Figure 2- When to discontinue Anti convulsive drug**
was scored from 0 to 3 to represent the range from normal to severely abnormal; these were then added together to produce a total composite score, ranging from 0 to 12. A cutoff score of 4 or higher provided the greatest sensitivity and specificity for prediction of adverse neurologic outcome.

References