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Clinical and etiological assessment of neonatal seizures in term neonates

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Abstract
Neonatal seizures are common and may be the first manifestations of neurological dysfunction after a variety of insults. It is critical to recognize neonatal seizures to determine their etiology and to treat them. Neonatal seizures present with varying manifestations like generalized tonic, multifocal clonic and subtle activity. Newborn babies do not manifest febrile convulsions. Therefore, it is important to recognize the seizures and treat it, as delay in recognition and treatment may lead to brain damage. The time of onset of seizure has relationship with the etiology and prognosis. Hence based on above findings the present study was planned for Clinical and Etiological Assessment of Neonatal Seizures in Term Neonates.
The present study was planned in Department of Pediatric, SNCU, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar. In the present study 120 clinically diagnosed with the seizures before 28 days of life were evaluated. Clinical criteria for diagnosing neonatal convulsions were, (a) focal, multifocal, or generalised clonic movement (b) tonic posturing with or without abnormal gaze (c) subtle seizures and spontaneous paroxysmal repetitive motor or autonomic phenomenon like lip smacking, chewing, paddling, swimming, cyclic movements or respiratory abnormalities.
The data generated from the present study concludes that perinatal asphyxia is the most common cause of neonatal seizures among term neonates in our setup. The other causes followed in order are metabolic (hypoglycaemia, hypoglycaemia, hypomagnesaemia and hyperbilirubinemia), septicaemia, intracranial haemorrhages and brain malformations. Hypocalcaemia was the commonest biochemical abnormality in primary metabolic seizures. Biochemical abnormalities were commonly associated with other etiologies like asphyxia, intracranial hemorrhage and meningitis; hence these should be actively sought for and treated for optimal seizure control.

Keywords: clinical, etiological, neonatal seizures, term neonates, etc

Introduction
The most prominent feature of neurologic dysfunction in the neonatal period is the occurrence of seizures. Determining the underlying etiology for neonatal seizures is critical. Etiology determines prognosis and outcome and guides therapeutic strategies [1].
The neonatal period is limited to the first 28 days of life in a term infant. For premature infants, this term usually is applied until gestational age 44 weeks; ie, the age of the infant from conception to 44 weeks (ie, 4 wk after term).
Most neonatal seizures occur over only a few days, and fewer than half of affected infants develop seizures later in life. Such neonatal seizures can be considered acute reactive (acute symptomatic), and therefore the term neonatal epilepsy is not used to describe neonatal seizures [2].
Seizures in neonates are relatively common, with variable clinical manifestations. Their presence is often the first sign of neurologic dysfunction, and they are powerful predictors of long-term cognitive and developmental impairment. Most seizures in the neonate are focal, although generalized seizures have been described in rare instances.
What have been termed "subtle seizures" are more common in full-term than in premature infants. Video electroencephalogram (EEG) studies have demonstrated that most subtle seizures are not associated with electrographic seizures. Examples of subtle seizures include chewing, pedaling, or ocular movements, these movements are thought not be epileptic in nature and more commonly are an epi-phenomena of severe encephalopathy [3].
Clonic seizures: These movements most commonly are associated with electrographic seizures. They often involve 1 extremity or 1 side of the body. The rhythm of the clonic movements is usually slow, at 1-3 movements per second.
Tonic seizures: These may involve 1 extremity or the whole body. Focal tonic seizures involving 1 extremity often are associated with electrographic seizures.
Generalized tonic seizures often manifest with tonic extension of the upper and lower limbs and also may involve the axial musculature in an opisthotonic fashion. Generalized tonic seizures mimic decorticate posturing; the majority are not associated with electrographic seizures.
Myoclonic seizures: These may occur focally in 1 extremity or in several body parts (in which case they are described as multifocal myoclonic seizures).
Focal and multifocal myoclonic seizures typically are not associated with electrographic correlates. These movements are thought to be non-epileptic in nature and a reflection of severe encephalopathy.
The biochemical effects of neonatal seizures include derangements of energy metabolism. Energy-dependent ion pumps are compromised, and adenosine diphosphate (ADP) levels rise. The rise in ADP stimulates glycolysis with the ultimate increase in pyruvate, which accumulates as a result of compromised mitochondrial function.

Seizures occur when a large group of neurons undergo excessive, synchronized depolarization. Depolarization can result from excessive excitatory amino acid release (eg, glutamate) or deficient inhibitory neurotransmitter (eg, gamma amino butyric acid [GABA]).

Another potential cause is disruption of adenosine triphosphate (ATP)−dependent resting membrane potentials, which cause sodium to flow into the neuron and potassium to flow out of the neuron. Hypoxic-ischemic encephalopathy disrupts the ATP-dependent sodium-potassium pump and appears to cause excessive depolarization. It is an important cause of neonatal seizures [1, 4].

Seizures resulting from hypoxic-ischemic encephalopathy may be seen in term and premature infants. They frequently present within the first 72 hours of life. Seizures may include subtle, clonic, or generalized seizures.

Intracranial hemorrhage occurs more frequently in premature than in term infants. Distinguishing infants with pure hypoxic-ischemic encephalopathy from those with intracranial hemorrhage often is difficult. Subarachnoid hemorrhage is more common in term infants. This type of hemorrhage occurs frequently and is not clinically significant. Typically, infants with subarachnoid hemorrhage appear remarkably well.

Germinal matrix-intraventricular hemorrhage is seen more frequently in premature than in term infants, particularly in infants born prior to 34 weeks' gestation. Subtle seizures are seen frequently with this type of hemorrhage. Subdural hemorrhage is seen in association with cerebral contusion. It is more common in term infants. Metabolic disturbances include hypoglycemia, hypocalcemia, and hypomagnesemia. Less frequent metabolic disorders, such as inborn errors of metabolism, are seen more commonly in infants who are older than 72 hours. Typically, they may be seen after the infant starts feeding.

"Early-onset epileptic encephalopathy" refers to a syndrome in which seizures are refractory to medications and severe cognitive/developmental issues are present. In those patients in whom structural and metabolic causes have been ruled out, genetic mutations are increasingly recognized. These mutations occur in genes that code for ion channel subunits (such as SCN1A, SCN8A, KCNT1) and other nueronal proteins and enzymes (such as CDKL5, STXBP1) [5].

Intracranial infections (which should be ruled out vigorously) that are important causes of neonatal seizures include meningitis, encephalitis (including herpes encephalitis), toxoplasmosis, and cytomegalovirus (CMV) infections. The common bacterial pathogens include Escherichia coli and Streptococcus pneumoniae. While most cerebral malformations present with seizures at a later age, major malformation syndromes are important to consider. Lissencephaly, pachygyria, polymicrogyria, and linear sebaceous nevus syndrome can present with seizures in the neonatal period.

Benign neonatal seizure syndromes can be characterized by familial or idiopathic seizures. Benign familial neonatal seizures typically occur in the first 48-72 hours of life; the seizures disappear by age 2-6 months. A family history of seizures is usual. Development is typically normal in these infants.

Benign idiopathic neonatal seizures typically present at day 5 of life (ie, fifth day fits), with the vast majority presenting between days 4 and 6 of life. Seizures are often multifocal. Cerebrospinal fluid (CSF) analysis is usually unremarkable.

The incidence of neonatal seizures in the United States has not been clearly established, although an estimated frequency of 80-120 cases per 100,000 neonates per year has been suggested. The incidence of seizures is higher in the neonatal period (ie, the first 4 wk after birth) than at any other time of life [6].

Neonatal seizures by definition occur within the first 4 weeks of life in a full-term infant and up to 44 weeks from conception for premature infants. Seizures are most frequent during the first 10 days of life. Prognosis is determined by the etiology of the neonatal seizures. If the EEG background is normal, the prognosis is excellent for seizures to resolve; normal development is likely [7, 8].

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.

Pisani *et al* devised a scoring system for early prognostic assessment after neonatal seizures. Analysis of 106 newborns with neonatal seizures who were followed prospectively to 24 months' postconceptional age identified 6 independent risk factors for adverse outcome: (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 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 [9].

Neonatal seizures are a risk factor that markedly increases rates of long-term morbidity and neonatal mortality. The presence of neonatal seizures is the best predictor of long-term physical and cognitive deficits. Acute neonatal seizures should be treated aggressively, although controversy exists as to the optimal treatment for them [11].

When clinical seizures are present, a rigorous workup to determine an underlying etiologic cause should be initiated quickly. Electrolyte imbalances should be corrected through a central venous site. Hypocalcemia should be treated cautiously with calcium, since leakage of calcium into subcutaneous tissue can cause scarring.

When an inborn error of metabolism is suspected, discontinue feeding, since feeding may exacerbate the seizures and encephalopathy. Institute intravenous solutions. Once these issues have been addressed, antiepileptic drug (AED) therapy should be considered. Phenobarbitone is the initial drug of choice. If seizures persist, the use of phenytoin should be considered.

Patients with seizures resulting from intracranial hemorrhage should have head circumference measurements performed daily. A rapid increase in head circumference may indicate hydrocephalus.

Seizure medication concentrations should be monitored during the acute period. These drugs often are discontinued between ages 3 and 6 months if further seizures have not occurred. A trend toward earlier discontinuation has met with good results. A general recommendation is to use

AEDs for 3 months, but electroencephalography may be helpful in deciding when to stop AEDs. If the patient remains seizure free, then medications may be tapered gradually. If the patient is on 2 AEDs, then one should be tapered first before considering withdrawal of the other.

If seizures recur, then the patient should be placed back on AEDs. Since phenobarbitone and phenytoin have disadvantages, including long-term side effects and, for phenytoin, difficulty maintaining levels, other medications may be considered. Some options include levetiracetam, oxcarbazepine, and topiramate.

Neonatal seizures are common and may be the first manifestations of neurological dysfunction after a variety of insults. It is critical to recognize neonatal seizures to determine their etiology and to treat them. Neonatal seizures present with varying manifestations like generalized tonic, multifocal clonic and subtle activity. Newborn babies do not manifest febrile convulsions. Therefore, it is important to recognize the seizures and treat it, as delay in recognition and treatment may lead to brain damage. The time of onset of seizure has relationship with the etiology and prognosis. Hence based on above findings the present study was planned for Clinical and Etiological Assessment of Neonatal Seizures in Term Neonates.

Methodology

The present study was planned in Department of Pediatrics, SNCU, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar. In the present study 120 clinically diagnosed with the seizures before 28 days of life were evaluated. Clinical criteria for diagnosing neonatal convulsions were [12], (a) focal, multifocal, or generalised clonic movement (b) tonic posturing with or without abnormal gaze (c) subtle seizures and spontaneous paroxysmal repetitive motor or autonomic phenomenon like lip smacking, chewing, paddling, swimming, cyclic movements or respiratory abnormalities.

Criteria for the various other metabolic / biochemical derangement are defined as follows [13]. Hyponatremia was serum sodium is < 130 meq/L, Hypernatremia was serum sodium > 150 meq/L and normal range 130- 150 meq/L. Hypomagnesaemia defined as serum magnesium level < 1.5 mg/dl, and normal range is 1.5 - 1.8 mg/dl, measured by atomic absorption spectrophotometry. Hypokalemia was serum potassium less than 3.5 meq/l and normal range is 3.5 – 5.5 meq/l. Benign fifth day fits occur between 2-5 days of life in otherwise healthy newborn with normal EEG and spontaneous recovery.

All the patients were informed and consent given by them. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Neonates (first 28 days of life) presenting with at least one of the following clinical type of seizures: Generalized tonic seizures, Multifocal clonic seizures, Focal clonic seizures, Myoclonic seizures, With or without accompaniment of subtle motor, movements, apnea or autonomic changes or the sole combination of subtle motor and autonomic manifestations were included in the study group.

Exclusion Criteria: Neonates with isolated brain release phenomenon, apnea or paroxysmal autonomic changes, i.e., only subtle motor moments or apnea without tachycardia or hypertension were excluded from the study. Jitteriness in neonates, Tetanic spasms in neonates.

Results & Discussion

Clinical seizures are defined as paroxysmal alteration in the neurological function i.e., behavioral, motor and/or autonomic function. The incidence of seizures is highest during the neonatal period, but clinical diagnosis is often difficult, thereby making it difficult to estimate the true incidence of neonatal seizures. Seizures are often the first sign of neurological dysfunction in the newborn, but their clinical presentation is quite variable often presenting only as subtle seizures in the form of chewing, lip smacking, fluttering of eyelids, staring look, etc.

Volpe [14] has classified seizures into five clinical types, viz. subtle, multifocal clonic, focal clonic, generalized tonic and myoclonic. Moreover, neonatal seizures are difficult to investigate and consequently determination of etiology and initiation of therapy may be delayed resulting in poor neurological outcome. Neonatal seizures can be due to various causes such as hypoxic-ischemic encephalopathy, intracranial hemorrhage (ICH), meningitis, hypoglycemia, hypocalcemia, congenital malformation, etc. Though electroencephalography (EEG) provides a useful noninvasive test to diagnose neonatal seizures and evaluate degree of perinatal damage to brain and long-term prognosis, yet its interpretation is influenced by variations in normal maturation process of brain.

Neonatal seizures present with varying manifestations like generalized tonic, multifocal clonic and subtle activity. Newborn babies do not manifest febrile convulsions. Therefore, it is important to recognize the seizures and treat it, as delay in recognition and treatment may lead to brain damage. The time of onset of seizure has relationship with the etiology and prognosis. For example, birth asphyxia usually presents in the first three days of life whereas meningitis presents after first week. The incidence rate was 2.6 per 1000 live births, 2.00 for term neonates, 11.1 for preterm neonates, and 13.5 for infants weighing < 2500 at birth [15]. If baby convulse within hours of delivery, it signifies poor prognosis and brain damage.

Common causes of convulsions in newborn are hypoxic ischemic encephalopathy, cerebral infarction and stoke intra cranial hemorrhage, metabolic disturbances, Intra cranial infections, and undetermined, etc. Tonic seizure and myoclonic seizures were associated with unfavorable outcome and found in infants with hypoxic ischemic encephalopathy and intra cranial hemorrhage. Most common Biochemical abnormality associated with neonatal convulsion is hypocalcemia, hypoglycemia, hypomagnesemia, Hyponatremia. hypogiycaemia in 50% cases associated with unfavourable outcome.

Table 1: Basic Detail

Parameters	No. of Cases
Sex	
Males	63
Females	57
Onset of Seizures	
Day of life	No. Of cases
1	39
2	28
3	15
4	10
5	4
6	10
7	10
> = 8	4
Total	120

Table 2: Type of Seizures

Type of Seizures	No. of Cases
Focal clonic	41
Subtle	35
Myoclonic	20
Focal tonic	12
GTCS: Generalized clonic tonic seizures	6
Multi Focal	6
Total	120

Table 3: Aetiology

Aetiology	No. of Cases
HIE	48
Sepsis	27
Hypocalcaemia	16
Hypoglycaemia	9
Hypomagnesemia	5
Intracranial Haemorrhage	5
Hyperbilirubinemia Kernicterus	5
Brain malformation	5
Drug withdrawal	0
Total	120

The data appear to indicate that much caution should be used in attributing an epileptic origin to many subtle clinical phenomenon, particularly in full-term infant and particularly if these phenomenon are the only manifestation of seizure in the infant. Although apnea has been demonstrated as a seizure manifestation in the premature newborn, vast majority are nonepileptic in origin.

Lakhra Mahaveer *et al*., [16] also reported that subtle seizures were the commonest. But in a study of neonatal seizures by Soni Arun *et al*., generalized tonic seizure was commonest type of seizure, followed by subtle seizures. In contrary to older children and adults, neonates present with subtle and generalized tonic seizures more commonly because of immaturity of central nervous system and more mature limbic system compared to other parts of CNS in neonates [17]. Subtle seizures are difficult to recognize and also difficult to interpret, as they may be normal neonatal activity and one should be careful in assigning subtle movements as seizures in neonates [18].

Ajay kumar *et al* in his study on clinico-etiological and EEG profile of neonatal seizures has found out the overall incidence to be 11.7/1000 live births with majority being in preterm babies (6.14%) compared to term babies (0.69%) [19]. According to a study conducted by Yadav *et al*. [20] in Uttar Pradesh, cumulative frequency of neonatal convulsion was 5.52% whereas similar study by Aziz *et al* has found out the cumulative frequency being 3.9% [21].

However, the incidence of neonatal seizures is more common in preterm than term babies and much more common in very low birth weight babies which was supported by various studies. In a study by Ronen *et al* and Gabriel *et al*. [22], they observed Clinical neonatal seizures occur 6 times more often in preterm infants than in term infant and Scher and Aso *Et al* in their study also has found the relative incidence is higher in premature infants less than 30 weeks gestation, occurring in 3.9% of these neonates compared with 1.5% of older infants.

Recognition of etiology is often helpful in prognosis and treatment. Studies suggest that neonatal seizures and their etiology have a significant impact on the developing brain; however, in clinical practice at neonatal intensive care units (ICU), in developing countries where synchronised video-EEG monitoring is practically non-existent, clinical observation becomes the key to the diagnosis.

These transient abnormalities are easily treatable when identified early and are associated with good prognosis. Hence biochemical work up should be done in all neonates with seizures and should be included as the first line of investigations in all cases. Early correction of these biochemical abnormalities help in preventing the further occurrence of seizures and also helps in avoiding over use of anticonvulsants which may be unnecessary in some cases. Further early correction of these metabolic disturbances improves the prognosis and outcome of the neonate and also prevent the long-term neurological sequelae associated with it.

In our study, we have identified neonatal seizures based on clinical criteria alone. In our setup where continuous video EEG monitoring is not available, which is necessary for confirming abnormal electroencephalogram discharge, there may be chances that we could have missed the electrographic seizures, so that the real magnitude of neonatal seizures is not known. Moreover, there may be overdiagnosis or underdiagnosis of cases based on interobserver variation and lack of continuous in-function cerebral monitor.

Conclusion

The data generated from the present study concludes that perinatal asphyxia is the most common cause of neonatal seizures among term neonates in our setup. The other causes followed in order are metabolic (hypoglycaemia,

hypoglycaemia, hypomagnesaemia and hyperbilirubinemia), septicaemia, intracranial haemorrhages and brain malformations. Hypocalcaemia was the commonest biochemical abnormality in primary metabolic seizures. Biochemical abnormalities were commonly associated with other etiologies like asphyxia, intracranial hemorrhage and meningitis; hence these should be actively sought for and treated for optimal seizure control.

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