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Clinico etiological study of seizures in neonates

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Abstract
Seizures in newborns are quite conspicuous in its varied clinical presentation and the diagnosis is frequently difficult. Recognition of these seizures early can help in early initiation of treatment for maximum preservation of neurologic function. The study was conducted at a teaching hospital in Odisha from July 2014-June 2016.alll neonates who were admitted with seizure or developed seizure during hospital stay were included in this study and extremely low birth weight babies, babies with multiple congenital anomalies are excluded from the study. Observed seizure patterns were recorded. All neonates were subjected to simple, less expensive, easily available investigations as complete blood count, band cell count, micro ESR, CRP, Immature/total neutrophil ratio, Glucose, Sodium, Calcium, Magnesium, CSF study, Cranial USG. Perinatal Asphyxia was found to be the commonest cause of seizure in neonates in our study (60% of cases) followed by sepsis/meningitis (15%) and presents within first 48hrs of life. Most frequent type of seizure pattern observed in our study is subtle variety followed by multifocal clonic type. Seizure on day 1 is most commonly due to perinatal asphyxia, similarly seizures after day 7 were found to be due to Sepsis/Meningitis. Most important determinant of neonatal mortality was due to perinatal asphyxia and sepsis. Only single anticonvulsant Phenobarbitone was used in 74.54% cases, 15% babies require 3 or more anticonvulsants.

Keywords: Neonate, neonatal seizure, perinatal asphyxia

Introduction
Seizures, that represents brains final common response to insult, occur more frequently in neonatal period than at any other parts of life. They represent the most distinctive signal of neurological disease in newborn period. The vulnerability of neonatal brain to seizures is thought to be due to combination of enhanced excitability with an abundance of NMDA binding sites and low levels of inhibitory neurotransmitter GABA. The precise frequency of neonatal seizures is difficult to delineate. Prompt diagnosis, investigation to know the cause and treatment are vital as delayed recognition of a treatable cause can have a significant impact on the future neurodevelopmental outcome.

Seizures in neonates are quite conspicuous in its multivariate clinical presentation and the diagnosis is frequently difficult. Despite rapid advancement in the electrophysiological and neuroimaging studies, many have felt the need of recognition of seizure clinically as they may be hardly accompanied by any significant changes in investigation but failure to recognize them clinically, may further complicate the problems on its own way [1].

As regards the etiological factors of seizure, they are many. Some of them require multiple sophisticated investigations, while others can be diagnosed clinically with a few simple investigations. Thus in present perspective neonatal seizure deserves intensive investigation and comprehensive research. But paucity of work in this field prompted us to undertake this study.

Methodology
This prospective observational study was conducted at the NICU of a tertiary care teaching hospital in Odisha. Written informed consent was taken from the parent before enrollment of their neonates in the study. The study period was from July 2014-June 2016. All the neonates who were admitted with seizure or developed seizure subsequently during hospitalization period were included in the study.

However following cases were excluded from the study

1) Jitteriness in newborn
2) primary apnea of cardio respiratory origin with concomitant Bradycardia
3) Extreme Low birth weight babies as clinical recognition of seizure is very difficult
4) Neonates with multiple congenital anomalies

All the mothers of neonates with seizure were carefully interviewed regarding age, parity, antenatal checkups, any antenatal risk factors as pregnancy induced hypertension, antepartum hemorrhage, Fever with rash, bleeding per vaginum, Gestational diabetes, drug intake, addiction. Past obstetric history, histories of seizure in family members or during neonatal period in earlier sibling were enquired. History was obtained for mode of delivery (Vaginal, Caesarean section, instrumental delivery), resuscitation details, Apgar score if available, time of cry after birth, abnormal movement/seizure (onset, duration, pattern). Birth weight was recorded by digital electronic weighing scale standardized up to 3 decibel points. Gestational age was determined from the last menstrual period or from 1st trimester Ultrasound if LMP not available or by modified Ballard scores assessment.

A thorough physical examination was carried out on all neonates, in naked state under daylight. Special vigilance was exercised on detection of rash, naevi or vascular malformation, cataract, organomegaly, neurological examination.

Observed seizure pattern as notified prior to intervention was recorded. Volpe's clinical classification [2] of subtle, clonic, multifocal clinic and myoclonic varieties was followed.

All the neonates were investigated with simple, less expensive and easily available investigations. Venous blood sample was collected after the seizure prior to therapy. The investigations include CBC, micro ESR, CRP, immature to total neutrophils ratio (I/T ratio), glucose, calcium, sodium, magnesium, CSF cytological & biochemical study/gram stain, culture. Cranial USG was done in all babies with seizure. Diagnosis of sepsis was done if 3 or more abnormalities are present I/T ratio >2, TLC <5000/cmm, mESR >10mm 1st hr, positive CRP >10mg/lt. Meningitis was considered in cases of sepsis on the basis of basis of low glucose, raised protein and increases CSF cell count. Cases with raised protein without low glucose with or without minimal cellular response in CSF were considered as Encephalitis.

All the babies are followed up even after discharge to assess long term outcome.

Results

Total 140 babies with neonatal seizure were admitted during the study period among which 108 (77.14%) babies were boys and 32 were girls (22.86%), 40 babies were Preterm (28.5%), 96 (68.57%) were term and 4 (2.86%) babies were post term, 88 (62.85%) babes weigh more than2.5kg, 47(32.57%) between 1.5-2.5kg and 5 (3.58%) babies were in< 1500gm category. Out of these 140 babies, 48 babies were deliveredvagsedinally, 8 by forceps, 18 by vacuum extraction, and 56 by LUCS.

Perinatal asphyxia was found to be the most common cause of seizure in 60% cases among all gestational age categories followed by sepsis/meningitis (15%) and metabolic causes (Hypoglycemia 5.7%, Hypocalcemia 5%). No cause was detectable in 7.1% cases. (Table 1)

Table 1: Etiology of neonatal seizures and distribution in various gestational ages

Etiologies	Preterm (%) n=40	Term (%) n=96	Post term (%) N=4	Total (%)
Perinatal asphyxia	16(19.04)	64(76.19)	4(4.77)	84(60)
Infection				
• Sepsis	2 (33.33)	(66.66)	0	6(4.28)
• Meningitis	4(26.66)	11(73.33)	0	15(10.72)
Primary metabolic				
• Hypoglycemia	3(37.5)	5(62.5)	0	8(5.72)
• Hypocalcemia	2(28.57)	5(71.43)	0	7(5.0)
• Hyponatremia	1(100)	0	0	1(0.71)
Intracranial hemorrhage	6(100)	0	0	6(4.2)
Bilirubin induced Neurologic damage (BIND)	2 (66.66)	1(33.33)	0	3(2.14)
Unknown	4(40)	6(60)	0	10(7.14)
Total	40	96	4	140(100)

Seizure begin within the first week of life in 125 cases (89.3%) and 80.7% cases in first 72hrs of life. Seizures on day 1 seen in 50 babies (35.71%cases) and perinatal asphyxia were the commonest cause of day 1 seizure. Day 2 seizure was seen in 39 babies (27.85%) and asphyxia again is the leading cause of day2 seizure followed by metabolic cause (hypoglycemia, hypocalcemia, hyponatremia). Seizures after day 7 of life was observed in 15 babies (10.7%) and sepsis was the cause in all of them. (Table 2)

Table 2: Day of Seizure onset in different etiological categories

Etiology	Day 1	Day 2	Day3	Day 4-7	Day 8-14	Day 15-28
Perinatal asphyxia n=84	48	28	8	0	0	0
Infection n=21	0	2	1	3	9	6
Hypoglycemia n=8	0	3	4	1	0	0
Hypocalcemia n=7	0	1	2	4	0	0
Hyponatremia n=1	0	1	0	0	0	0
Primary ICH n=6	1	3	2	0	0	0
Unknown n=10	1	1	6	2	0	0
Total (%)	50(35.71)	39(27.85)	24(17.14)	12(8.57)	9(6.42)	6(4.28)

Subtle seizure was the most common clinical type of seizure in 52 babies (37.14%) followed by multifocal clonic 36(25.71%) and focal clonic 25(17.85%) cases. Myoclonic seizure was the least common type of seizure noted in 7.14% babies in our study. Subtle seizures were the commonest form of seizure in preterm babies. Multi focal clonic, focal clonic and tonic seizure pattern occurred more commonly in term babies. (Table 3)

Table 3: Clinical Pattern associated with different etiologies

Etiology	Subtle (%)	Focal Clonic (%)	Multifocal clonic (%)	Myoclonic (%)	Tonic (%)
Perinatal Asphyxia (n=84)	37(44.04)	12(14.28)	20(23.8)	7(8.33)	8(9.52)
Meningitis n=15	4(26.6)	2(13.33)	5(33.33)	2(13.33)	2(13.33)
Sepsis (n=6)	3 (50)	1(16.66)	2(33.33)	0	0
Hypoglycemia n=8	1(12.5)	5(62.5)	1(12.5)	0	1(12.5)
Hypocalcemia n=7	1(14.28)	2(28.56)	3(42.85)	0	1(14.28)
Intracranial Hemorrhage n=6	3(50)	0	1(16.66)	0	2(33.33)
BIND n=3	1(33.33)	0	1(13.33)	0	1(13.33)
Unknown n=10	2(20)	2(20)	3(30)	1(10)	2(20)
Total n=140	52(37.14)	25(17.85)	36(25.71)	10 (7.14)	17(12.14)

Out of 130 cases of seizure where Transcranial USG was performed, subependymal hemorrhage was found in 10 (7 Preterm, 3 term 0, Intraparenchymal hemorrhage in 6 (4 preterm, 2 term), Cerebral edema in 29 (19term, 10 preterm), cerebral infarction in 2(term) and subdural collection in 1 (term) baby respectively.

Death occurred in 32 cases (22.85%) with 25 cases belonging to asphyxia group. It was observed that 48.57% cases were neurologically normal at the time of discharge. Single episode of seizure was seen in 78(55.71%) cases, 2episodes in 33(23.5%) and 3 or more episode of seizure in 29 (20.7%) babies.

Anticonvulsant therapy was used in 110(78.57%) babies, 82babies required only single anticonvulsant (Inj Phenobarbitone), 11(10%) babies required 2anticonvulsants (Inj phenobarbital, Inj Fosphenytoin) and 17 (15.45%) babies required 3 or more anticonvulsant (Inj phenobarbital, Inj Fosphenytoin, Inj Levetiracetam/Inj Midazolam infusion).

Discussion

This prospective study on clinic etiological profile of neonatal seizure included 140 cases. There was male preponderance (77.1%) similar to the study of Srinivas *et al* [3] who postulated that genetically males were prone to develop convulsion than females. Birth asphyxia was found to be the commonest cause of neonatal seizure in this study in 60% of cases, Volpe *et al* [4] Observed encephalopathy from asphyxia is the cause in 60-65% cases, Levene *et al* [5] Study found HIE as the case in53% cases. Our study doesn't corroborate with studies by Kumar *et al* [6], Lien *et al* [7], Goldberg *et al* [8] where 45%, 37% and 16% of neonatal convulsion were due to HIE respectively. The incidence of primary intracranial hemorrhage was 4.28% in our study in contrast to the studies by Levene *et al* [5] (17%), Andre *et al* [9] (14%), Lien *et al* [7] (12%) and Volpe *et al* [4] (10%). Our study detected primary metabolic abnormality as the cause in 11.42% cases. Out of total 16 cases with primary metabolic alteration, hypoglycemia was seen in 8/16(50%), hypocalcaemia seen in 7/16(43.45%) and hyponatremia in 1/10 (6.255) infants. But in studies from Kumar *et al* [6] primary metabolic disorders was seen in 25.75%cases (9/35) with isolated hypoglycemia/ hypocalcaemia in 8.57%cases each, hyponatremia/ hypomagnesaemia in 2.85% cases respectively. Incidences of hypoglycemia/hypocalcaemia were 3% each as per Volpe *et al* study.

Infection was the cause of seizure in 14.99% cases in our study and 10.7% are due to meningitis. Studies by Kumar *et al* [6], Painter *et al* [10] describes infection as the cause in 10%, 4% respectively.

Bilirubin induced neurologic damage (BIND) was seen in 3/140 (2.1%) cases in our study. No case of seizure due to narcotic withdrawal was reported, as these practices are distinctly uncommon in mothers in this region. Also there was no case of cerebral malformation (probably because of exclusion of babies with multiple congenital anomalies from study group), accidental injection of local anesthetic into scalp, 5th day fits and familial neonatal seizure in our study. The exact cause remains undetermined in 7.1% cases. In Volpe *et al* [4] and Brown *et al* [11] Series incidence of such idiopathic seizures were reported to 5% and 9% respectively. 57.14% cases of birth asphyxia had seizure on day1, which corroborates well with study of Volpe *et al* who account for 60%of case on day 1. Infection was the cause noted in seizure after day 7 of life in all cases corroborating to the observation of Kumar *et al* [5].

Birth asphyxia and meningitis were associated with all seizure patterns. Commonest seizure pattern in our study was subtle type (44%), followed by multifocal clonic (23.895) and focal clonic in (14.3%) cases. Volpe *et al* observed similar pattern of seizure.

Death was the outcome in 22.85% cases of seizure with perinatal asphyxia as the leading cause followed by sepsis. Bharadwaj *et al* [12] had also found these 2 factors to be the most important determinant of neonatal mortality.

Conclusion

A neonate with convulsion is an emergency and it is important to recognize early so that treatment can be initiated promptly for maximum preservation of neurological function. From our study it was concluded that perinatal asphyxia is the commonest cause of seizure in neonate and presents within first 48hrs of life. Most of the seizures occur on day 1. Most frequent type of seizure pattern observed is subtle variety. Most common seizure pattern in asphyxia is subtle type. Infection and metabolic conditions like hypoglycemia, hypocalcemia produce mostly clonic pattern of seizure. Leading cause of death in neonatal seizure during hospital stay in relation to etiologies are perinatal asphyxia and Infection.

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Conflict of interest: There is no conflict of interest among the authors. There is no financial burden to family neither financial incentive to parents for giving consent to be included in the study.

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