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Etiological Profiling of Neonatal Seizures in a Tertiary Care Center

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Abstract:
Background: *Seizures are more common in the neonatal period than during any other time throughout life. Compared with seizures at older ages, neonatal seizures differ in etiology, semiology, and electroencephalographic signature, and can be refractory to antiepileptic drugs that are effective in other age populations.*
Objectives: *To find out the etiologies of seizures in neonates admitted in a Tertiary care hospital.*
Materials and Methods: *The study was cross sectional, observational & analytical in nature, performed over a period of 1 year. Data were analyzed in microsoft excel using standard statistical techniques.*
Results: *Major etiologies for neonatal seizure were Hypoxic ischaemic encephalopathy 55%, Early Onset Neonatal Sepsis 11%, Late Onset Neonatal Sepsis ate 18%, Bilirubin encephalopathy 4%, malformation 2%, dyselectrolytemia 4%, hypoglycemia 3%*

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I. Introduction

The immature brain seems more prone to seizures than the more mature brain. Seizures are more common in the neonatal period than during any other time throughout life. Seizures in the neonatal period are also the most common neurological emergency and are associated with high mortality and morbidity. Compared with seizures at older ages, neonatal seizures differ in etiology, semiology, and electroencephalographic signature, and can be refractory to antiepileptic drugs that are effective in other age populations.

Causes of Neonatal Seizures according to common age of presentation [1]
AGES 1-4 DAYS 1. Hypoxic–ischemic encephalopathy 2. Drug withdrawal, maternal drug use of narcotic or barbiturates 3. Drug toxicity: lidocaine, penicillin 4 .Intraventricular hemorrhage 5. Acute metabolic disorders Hypocalcemia, Hypomagnesemia,Hyponatremia or Hypernatremia, SIADH Sepsis Hypoglycemia- Perinatal insults, prematurity, SGA, Maternal diabetes, Hyperinsulinemic hypoglycemia 6. Inborn errors of metabolism Galactosemia, Hyperglycinemia, Urea cycle disorders 7.Pyridoxine deficiency and pyridoxal-5-phosphate deficiency (must be considered at any age)
AGES 4-14 DAYS 1. Infection 2. Meningitis (bacterial) Encephalitis (enteroviral, herpes simplex) 3. Metabolic disorders Hypocalcemia- Diet, milk formula Hypoglycemia, persistent, Anterior pituitary hypoplasia, pancreatic islet cell tumor, Beckwith syndrome Inherited disorders of metabolism Galactosemia, Fructosemia, Leucine sensitivity,

Hyperinsulinemichypoglycemia,hyperinsulinism, hyperammonemia syndrome 4. Drug withdrawal, maternal drug use of narcotics or barbiturates 5. Benign neonatal convulsions, familial and nonfamilial 6. Kernicterus, hyperbilirubinemia 7. Developmental delay, epilepsy, neonatal diabetes syndrome
AGES 2-8 WK 1. Infection Herpes simplex or enteroviralencephalitis,Bacterial meningitis 2. Head injury Subdural hematoma,Child abuse 3. Inherited disorders of metabolism Aminoacidurias, Urea cycle defects, Organic acidurias, Neonatal adrenoleukodystrophy 4. Malformations of cortical development Lissencephaly, Focal cortical dysplasia 5. Tuberous sclerosis 6. Sturge-Weber syndrome

OBJECTIVES:
To find out the etiologies of seizures in neonates admitted in a Tertiary care Hospital along with profiling of use of Antiepileptic Drugs & briefing of Short term outcome.

II. Material And Methods

The study was cross sectional, observational & analytical in nature, performed over a period of 1 year (May 2016 to April 2017). Data were collected in a predesigned proforma. We organized & analyzed data in Microsoft Excel 2010 using standard statistical techniques.

III. Results

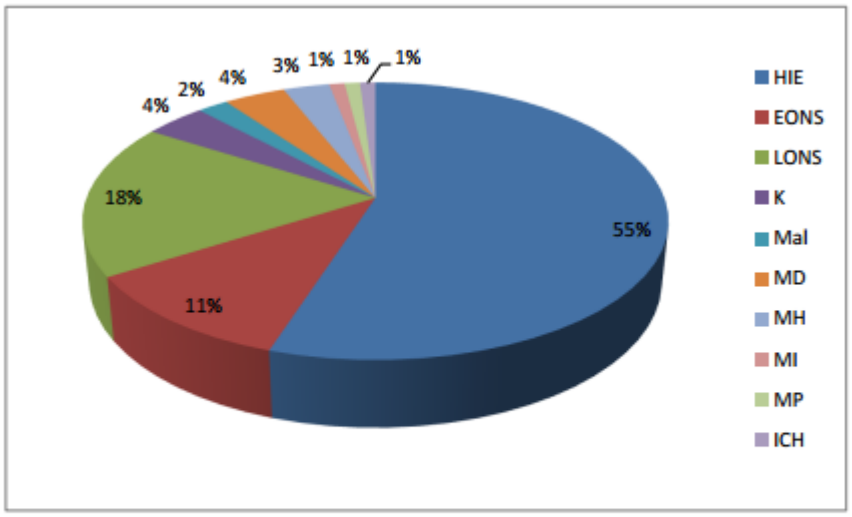
Title: Distribution of study population according to etiology of neonatal seizures (N-100)

Table no.1

Etiology of seizure	Frequency	Percentage
Hypoxic ischaemic encephalopathy (HIE)	55	55 %
Early Onset Neonatal Sepsis (EONS)	11	11%
Late Onset Neonatal Sepsis (LONS)	18	18%
Bilirubin encephalopathy (K)	4	4%
Malformation (Mal)	2	2%
Dyselectrolytemia (MD)	4	4%
Hypoglycemia (MH)	3	3%
Inborn errors of metabolism (MI)	1	1%
Pyridoxine deficiency (MP)	1	1%
Intracranial haemorrhage (ICH)	1	1%

In the present study major etiologies for neonatal seizure were Hypoxic ischaemic encephalopathy 55%, Early Onset Neonatal Sepsis 11%, Late Onset Neonatal Sepsis ate 18%, Bilirubin encephalopathy 4%, malformation 2%, dyselectrolytemia 4%, hypoglycemia 3%, inborn errors of metabolism 1%, pyridoxine deficiency 1% and intracranial hemorrhage 1%. The baby categorised as having inborn errors of metabolism had Non Ketotic Hyperglycinemia. The next pie chart explains the table.

Figure1:



Distribution of study population according to etiology of neonatal seizures

Title: Distribution of study population according to number of anticonvulsants use for control of seizure (N-100)

Table no. 2:

No. of anticonvulsants used	Frequency	Percentage
Nil	10	10%
1	66	66%
2	12	12%
More than 2	12	12%

10% of the babies in the study population required no anticonvulsants, these are the babies with hypoglycemia, dyselectrolytemia and 3 babies with sepsis who also had hypoglycemia. In 66% of the babies only a single drug (we start with phenobarbitone) was required, in 12% a second drug (phenytoin) was added and in the rest 12% three or more drug

Title: Distribution of study population according to duration of stay in hospital in number of days (N-100)

Table no. 3:

No. of days of stay	Frequency	Percentage
1 to 6 days	33	33%
7 to 13 days	17	17%
14 to 20 days	9	9%
21 days or more	41	41%

41% of our babies had a hospital stay of 21 days or more, these were mostly the babies with sepsis requiring prolonged course of antibiotics and few babies with severe HIE with neurodeficit who were having difficulty with feed establishment. 33% required less than 7 days to be discharged, these were mostly the babies with favourable prognosis.

Title: Distribution of study population according to short term outcome (N-100)

Table no.: 4

Outcome	Frequency	Percentage
No neurological deficit (NND)	67	67%
With neurological deficit (ND)	23	23%
Death (D)	10	10%

The outcomes of the babies were determined at discharge. 67% of the babies had no neurological deficit, 23% had neurological deficit and 10% were dead. The babies with no neurological deficit are considered to be having a favourable outcome and those with neurological deficit and were dead had poor outcome.

IV. Discussion

Etiology of neonatal seizures was identified in 100% cases as was identified in 99% cases by Malik BA et al[2]. It is concluded that neonatal seizures are rarely idiopathic, therefore, an extensive diagnostic work up is needed to establish the cause of seizures in the newborn period.[3] In the present study major etiologies for neonatal seizure were Hypoxic ischaemic encephalopathy 55%, EONS 11%, LONS 18%, kernicterus 4%, malformation 2%, dyselectrolytemia 4%, hypoglycemia 3%, inborn errors of metabolism 1%, pyridoxine deficiency 1% and intracranial hemorrhage 1%. In the study done by Shah et al on neonatal seizures major etiologies were birth asphyxia 44%, septicemia 11%, meningitis 11%, hypocalcemia 11% and hypoglycemia (22%).[4] Work done by Ruma et al revealed perinatal asphyxia in 56.86% neonates, septicemia 15.76%, meningitis 11.76%, kernicterus 3.92%, neurometabolic

Gestational age						
Present study	Shahjad et al 5	Manoel RR et al				
Pretem	Term	Pretem	Term	Pretem	Term	
CLONIC	13%	25%	5%	40%	14.4%	11.5%
MYOCLONIC	1%	-	-	3%	2.9%	3.8%
SUBTLE	8%	25%	2%	19%	7.7%	51.9%
TONIC	7%	17%	3%	28%	9.6%	19.2%

disorder 3.92%, TORCH infections 1.96%, Hypoglycemia 19.5%, Hypocalcemia 15.7%.Maya et al found etiology of neonatal seizures as HIE in 37.8% babies, hypoglycemia in 19.3%, meningitis in 5.9%, intracranial bleed 9.6%,hypocalcemia in 2.2%, neonatal stroke 3.7% and IEM in 1.5%.[5]In a study done by Ajay et al major etiology of seizure was perinatal asphyxia in40% neonates, hypoglycemia in 10%, hypocalcemia in 9%, hypernatremia 1%hypoglycemia with hypocalcemia in 1% and meningitis in 7% . Few other causes were intracranial bleed,bilirubinenecephalopathy, polycythemia brain malformation.[6]In the study done by Sahana et al (N-109) perinatal asphyxia was the major etiology (57.80%), second common etiology were infections at 14.67%,hypoglycemia was present in 9.17% ,hypocalcemia 6.4%, ICH 5.5%,kernicterus 1.8% and 4.58% were idiopathic.[7] Suryavanshi et al found HIE in 46.25%, hypoglycemia 16.25% , hypocalcemia5% , infections 11.25% and intracranial hemorrhage 18.75%.[8]

Comparison of aetiology with few other studies:-

Etiology	Present study	Shahjad et al 5	Malik et al 1	Park et al 2	Jin etal28	Sabzehei et al 15	Talebian et al 29
Birth Asphyxia	55%	46%	35%	32.9%	65%	34.3%	36%
Septicaemia/ Meningitis	29%	29%	34%	9.6%	-	24.5%	10%
Metabolic	9%	23%	12.5%	32.9%	5%	9.8%	38%

abnormalities							
Intracranial haemorrhage	1%	4%	9.5%	5.5%	10%	6.9%	11%
Kernicterus	4%	6%	4.5%	-	-	-	
Tetanus	-	5%	-	-	-	-	
Hydrocephalus	-	5%	1.5%	-	-	-	
Brain Malformation	2%	3%	1%	-	6%	-	5%
Fifth day fit	-	1%	1%	6.8%	3%	-	
Encephilitis	-	1%	-	-	-	-	
Birth trauma	-	1%	-	-	-	-	
Turner Syndrome	-	1%	-	-	-	-	

Thus it can be seen that HIE was found to be the commonest cause of neonatal seizure in most studies. Second most common cause was sepsis or meningitis except in few studies done by Park et al [9], Talebian et al[10], Suryavanshi et al[8] and Ajay et al 7 where metabolic or ICH were common than infections. The other causes had varying proportion in different studies. Most seizures in the asphyxiated newborn occurred in first 72 hours of life as in our study and studies done by Alcover et al[11] , Sood A et al[12] and Malik BA et al.1 HIE was the predominant aetiology in the full term (61.2%) babies with preterm babies having 34.5% of their seizures due to HIE. This is in contrast to the following two studies

1. Calciolari et al reporting neonatal asphyxia as the predominant aetiology in both premature and full term neonates.[13]
2. Hypoxic-ischemic encephalopathy causing seizures in 50–60% of neonates, independent of gestational age, according to Volpe.[14]

In the present study subtle seizure was the predominant variety (47.27%) in HIE followed by clonic (32.7%) and tonic (20%) variant. This is in contrast toreports by

1. Shahjad et al with clonic variety (54%) as the commonest type in HIE, followed by subtle (21.7%) and tonic (19.5%) variety were the next common type in HIE.[15]
2. Ajay K et al with clonic and tonic variety as the commonest HIE. [16]

V. Conclusion

In most of the cases, the causes of neonatal seizures were present. It is idiopathic in a small percentage of cases. However, to establish the exact cause of seizures, extensive work up is needed. Birth asphyxia, septicaemia with or without CNS infection and metabolic disorder were found to be the most common causes. Recognition of etiological factors is helpful in prognosis and treatment. The best outcome was seen with metabolic abnormalities as an etiological factor of neonatal seizures.

AUTHORSHIP INFORMATION:

DrGayen S: Study conceptualization; manuscript editing; DrSaha RP: data collection, analysis; Das PS: analysis and manuscript writing ; All authors approved final version of manuscript.

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