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NEONATAL SEIZURES;

TYPES, ETIOLOGY AND LONG TERM NEURODEVELOPMENTAL OUTCOME AT A TERTIARY CARE HOSPITAL.

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ABSTRACT… Objective: To study the types, etiology and long term neurodevelopmental outcome in neonates with seizures. **Study Design**: A descriptive cross-sectional study. **Place and Duration of Study**: PNS Shifa Naval hospital Karachi from Jan 2011 to Feb 2014. **Study Population**: Ninety six neonates of either gender presented with seizures at NICU PNS Shifa Naval hospital Karachi were studied. **Method**: All neonates with seizures were evaluated. The seizures were classified according to the simiology. They were investigated according to NICU protocol to confirm the underlying diagnosis and timely management. The patients after discharge were regularly followed up for one year to assess the long term neurodevelopmental outcome. **Results**: A total of 96 neonates with seizures were studied and it was observed that 60 (62.5%) were male babies and 56 (58.33%) were term with a male to female ratio of 1.6:1. Majority of the neonatal seizures were seen in 1st week of life (85%). The most common type of seizures was clonic 40 (41.67%) followed by subtle 20 (20.84%), mixed 16 (16.67%), tonic 10 (10.41%), myoclonic 5 (5.20%) and unclassified 5 (5.20%). Antiepileptics were used in 82 (85.41%) patients. Phenobarbitone 49 (59.76%) was most commonly prescribed drug. The most common cause of seizures was birth asphyxia 48 (50%) followed by metabolic 16 (16.68%), sepsis 10 (10.41%), intracranial hemorrhage 6 (6.25%), bilirubin encephalopathy 4 (4.16%), inborn errors of metabolism 2 (2.08%), birth trauma 2 (2.08%) and unknown etiology 5 (5.20%). 25 (26.04%) patients develop adverse neurodevelopmental outcome i.e. cerebral palsy with epilepsy 10 (40%) and cerebral palsy without epilepsy 05 (20%), developmental delay 10 (40%). Mortality in the study was 12 (12.5%). **Conclusions:** Clonic seizures are commonest in neonates apart from infants and children who have GTCS. The most common etiology of seizures in neonates is birth asphyxia. Phenobarbitone is still the most commonly prescribed antiepileptic. Quick assessment, timely diagnosis and aggressive management according to the etiology are necessary to prevent the morbidity and mortality associated with neonatal seizures. Long term neurodevelopmental outcome is worse in patients with birth asphyxia especially with low Apgar score at 5 minutes. Normal delivery and birth asphyxia were the major risk factors for cerebral palsy.

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INTRODUCTION

A seizure or convulsion is a paroxysmal, time-limited change in motor activity and/or behavior that results from abnormal electrical activity in the brain[1]. Occurrence of seizure is a symptom of an underlying neurological disease which may be a consequence of any systemic or biochemical disturbance[2]. Seizures are more common in the neonatal period than in any other stage and affects approximately 1% of all neonates[3].

Epileptic seizures are more frequent in the neonate than at any other time. The incidence of neonatal seizures is estimated to be between 1.5 and 5.5/1000 living births, its onset being during the first week in 80% of cases. Neonates may present with different types of seizures: clonic, tonic, myoclonic (axial, focal, erratic), epileptic spasms, and subtle seizures, including autonomic signs or automatisms[4]. Historically, neonatal seizures are divided into subtle, clonic, tonic and myoclonic seizures. Clonic and tonic seizures are further classified into focal and generalized types[5].

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Hypoxic-ischaemic encephalopathy is the most frequent cause of neonatal seizures in term babies followed by focal ischaemia (stroke), cerebral malformations and metabolic disturbances. In preterm neonates, intraventricular haemorrhage and infections cause most of the seizures reported in this group[6]. Lopes A et al identified etiology in 51.6% of neonates i.e. central nervous system bleeding (11 cases), hypoxic-ischemic encephalopathy (10 cases) and electrolytes disturbances (7 cases)[7].

The choice of anticonvulsants has been based on tradition rather than on the proven superiority of one agent over another. Although several anticonvulsants are available, phenobarbital remains the drug most frequently chosen as the initial agent in treatment.[8] Overall, for babies born at full term, typical current mortality rates being 10% (range: 7-16%). By contrast, the prevalence of adverse neurodevelopmental sequelae remains relatively stable, typically 46% (range: 27-55%). The strongest predictors of outcome are the underlying cause, together with the background electroencephalographic activity.[9]

This study aimed to determine the types, etiology and long term neurodevelopmental outcome in neonates with seizures. Neonatal seizures are a potentially life-threatening pediatric problem with a variety of causes. Thorough and timely evaluation of these patients is necessary to identify and treat the underlying etiology, therefore reducing potential morbidity and mortality. The present study was planned to determine the etiology of neonatal seizures in our setup to have an effective strategy for their management and also to assess the long term neurodevelopmental outcome along with prognosis.

PATIENTS AND METHODS

This descriptive cross-sectional study was carried out at Paediatric Department of PNS Shifa Naval hospital, Karachi from January 2011 to February 2014. The study population consisted of 96 neonates of army personnel and civilians admitted to NICU PNS Shifa hospital with seizures. All neonates of either gender from day 1 to 28th day of life with seizures were included in the study.

All the patients meeting the inclusion criteria were evaluated after informed consent of the parents. The study was approved by the PNS Shifa hospital Research and Ethics Committee. Jitteriness or sleep-related muscular activities and other non-seizures movements were differentiated from seizures on the basis of absence of ocular movements, absence of autonomic changes, normal sensorium and cessation of movements on holding the affected parts.

Detailed history especially gestational age, age of onset, duration and type of seizures, antenatal history of maternal fever with or without rash, gestational diabetes, pregnancy induced hypertension, endocrine disorders and maternal drug intake were taken. Natal and post-natal history was also taken in detail like place and mode of delivery, duration of labour, any need of resuscitation at delivery and Apgar score < 4 at 1 and 5 minutes of age. Obstetrical history of neonatal seizures in previous siblings, early neonatal deaths, jaundice and exchange transfusion was taken.

All neonates were examined in detail for vital signs, dysmorphic features, weight, head circumference, motor system, fontanelle, birth trauma, hepatosplenomegaly, cardiovascular and respiratory system, skin and fundoscopy findings were recorded on a data form.

Their initial relevant investigations included blood complete picture with peripheral film, C-reactive protein levels, blood glucose levels, arterial blood gases, renal function tests, liver function tests, serum calcium, serum phosphate, serum magnesium, ultrasound scan brain and cerebrospinal fluid examination for evidence of infection. Blood culture was done in selected cases to rule out infection. EEG and CT scan were performed according to the presentation to confirm the underlying cause of seizures. MRI brain, thrombophilia screen, plasma ammonia,

plasma lactate, TORCH antibody titre, urine for metabolic screening, chromosomal analysis and urine for non glucose reducing substances were carried out in selected cases to reach the specific diagnosis.

Hypoglycaemia was defined as blood glucose less than 40 mg/dl in premature and less than 45mg/dl in term babies while hypocalcaemia as serum calcium less than 7.5 mg/dl. CSF examination was considered abnormal when there were elevated CSF leukocytes, low CSF sugar, elevated CSF protein and/or positive smear for gram staining. The seizures were classified according to International League Against Epilepsy guidelines.[10]

The patients were managed initially with injection midazolam (3-doses were given at regular 5 minutes interval in patients with uncontrolled seizures). Injection phenobarbitone 20 mg/kg, injection phenytoin 20mg/kg or even continuous midazolam infusion was used in neonatal status epilepticus followed by maintenance doses of these antiepileptics. Other supportive measures such as intravenous fluids, metabolic abnormalities correction and oxygen therapy were usually given according to the underlying primary diagnosis. Seizures of patients not responding to above treatment had challenging dose of intravenous pyridoxine (200 mg).

Neonatal status epilepticus was defined as continuous seizure activity for at least 30 minutes or recurrent seizures lasting a total of >30 minutes without definite return to the baseline neurologic condition of the newborn between seizures. Patients who were discharged after stabilization were followed up after three months, six months and one year respectively in paediatric OPD. Their anthropometric measurements, neurodevelopmental examination were carried out every time to assess neurodevelopmental outcome. All data was analyzed using Statistical Package for Social Sciences (SPSS) version 15.0. Frequencies and percentages were calculated for all collected data.

RESULTS

A total of 96 patients fulfilling the inclusion criteria with seizures were evaluated and it was observed that 60 (62.5%) were male babies and 36 (37.5%) were female babies with a male to female ratio of 1.6:1. 56 (58.33%) were term and 40 (41.67%) were preterm babies. Neonatal seizures were seen in 1stweek of life in 82 (85.41%) of patients.

The most common type of seizures was clonic 40 (41.67%) followed by subtle 20 (20.84%), mixed 16 (16.67%), tonic 10 (10.41%), myoclonic 5 (5.20%) and unclassified 5 (5.20%). Antiepileptics were used in 82 (85.41%) patients. Injection midazolam was given in all 82 (85.41%) patients initially. Phenobarbitone 49 (59.76%), phenytoin 23 (28.04%) and midazolam infusion 10 (12.20%) were given in status epilepticus after initial three doses of injection midazolam at regular five minute intervals.

The most common cause of seizures was birth asphyxia 48 (50%) followed by metabolic 16 (16.68%), sepsis 10 (10.41%), intracranial hemorrhage 6 (6.25%), bilirubin encephalopathy 4 (4.16%), inborn errors of metabolism 2 (2.08%), birth trauma 2 (2.08%), pyridoxine deficiency 1 (1.04%), brain malformation 1 (1.04%), Down syndrome 1 (1.04%) and unknown etiology 5 (5.20%).

Etiology	Frequency (%)
Birth asphyxia	48 (50%)
Metabolic abnormalities	16 (16.68%)
Sepsis	10 (10.41%)
Intracranial hemorrhage	06 (6.25%)
Bilirubin encephalopathy	04 (4.16%)
Inborn errors of metabolism	02 (2.08%)
Birth trauma	02 (2.08%)
Pyridoxine deficiency	01 (1.04%)
Brain malformation	01 (1.04%)
Down syndrome	01 (1.04%)
Unknown etiology	05 (5.20%)
	N=96 (100%)

Table-I. Etiology of neonatal seizures

Of the 96 babies, 51 (53.12%) had normal occipitofrontal circumference while 43 (44.79%) had microcephaly and 2 (2.08%) had macrocephaly. 25 (26.04%) patients develop adverse neurodevelopmental outcome i.e. cerebral palsy with epilepsy 10 (40%) and cerebral palsy without epilepsy 05 (20%), developmental delay 10 (40%). All patients with cerebral palsy 15 (15.62%) had microcephaly. Out of cerebral palsy patients, 10 (66.66%) were SVDs while 5 (33.33%) were LSCS. Neurodevelopmental outcome was especially worse in 6 (6.25%) with a low Apgar score <4 at five minutes.

Ultrasound scan brain showed intracranial hemorrhage in 6 (6.25%) patients. EEG was positive in 15 (15.62%) while neuroimaging were diagnostic in other 16 (16.66%). The prognostic factors for long term neurodevelopmental outcome were mode of delivery, Apgar score at 5 minutes, resuscitation at birth, underlying etiology, status epilepticus, neuroimaging findings, number of antiepileptics and response to acute management. Mortality in the study was 12 (12.5%) despite aggressive and timely management.

DISCUSSION

The neonatal period is the most vulnerable of all periods of life for developing seizures, particularly in the first week from birth. They often signify serious underlying malfunction or damage to the immature brain and constitute a neurological emergency demanding urgent diagnosis and management[11].

There is a consistence male predominance of all types of seizures. The higher occurrence of seizures in males is not surprising as many of the underlying conditions are more frequent in males[12]. Male to female ratio was 2.1:1. Regarding gestational age, 65% were full-term, 31% were pre-term, and 4% were post-term[13]. The present study also showed a male predominance with male to female ratio of 1.6:1. As regards gestational age in the present study, 58.33% were term and 41.67% were preterm babies. Most (80%) neonatal seizures occur in the first 1–2 days to the first week of life[4]. The present study also showed that seizures occurred in 85.41% of patients in first week of life.

The most widely used scheme is by Volpe of five main types of neonatal seizure i.e. Subtle seizures (50%), Tonic seizures (5%), Clonic seizures (25%), Myoclonic seizures (20%), Non-paroxysmal repetitive behaviours.[14] The most common type of seizures in the present study was clonic 41.67% followed by subtle 20.84%, mixed 16.67%, tonic 10.41%, myoclonic 5.20% and unclassified 5.20%. In practice, phenobarbital still remains the drug of first choice for EEG confirmed or suspected seizures.[15] Wickstrom R et al studied and described the initiation of treatment of neonatal seizures, as well as choice of first-(phenobarbital) and second-line (midazolam) drugs[16]. Phenobarbitone was also the most commonly used antiepileptic in the present study.

Perinatal asphyxia (28.6%) and intracranial hemorrhage (17%) were the most common causes of neonatal seizures[17]. Neonatal seizures have a variety of causes such as birth trauma, asphyxia, congenital anomalies, metabolic disturbances, infections, and drug withdrawal or intoxication[18]. The present study showed that neonatal seizures were caused by birth asphyxia 50%, metabolic abnormalities 16.68%, sepsis 10.41%, intracranial hemorrhage 6.25%, bilirubin encephalopathy 4.16%, inborn errors of metabolism 2.08%, birth trauma 2.08% and unknown etiology 5.20%.

Neonatal seizures are not related to an increased risk to develop epilepsy. Epilepsy alone is a rare event and it usually complicates CP picture. Preterm VLBW infants have a greater risk to develop a psychomotor delay[19]. The present study revealed that 26.04% patients develop adverse neurodevelopmental outcome (cerebral palsy with epilepsy 40% and cerebral palsy without epilepsy 20%, developmental delay 40%). Home deliveries (RR, 3.80) and births attended by midwives (RR, 1.88) with an Apgar score 0 at 5 minutes had a significantly higher risk of neonatal seizures or serious neurologic dysfunction (P < .0001) than hospital births[20]. Neurodevelopmental

outcome was worse in patients with Apgar score <4 at 5 minutes in the present study. Cerebral palsy risk factors are considered from the prenatal, perinatal and neonatal period in children born at term[21]. Topp M et al has reported that LSCS is a prognostic factor for developing cerebral palsy[22]. The present study showed that normal delivery and birth asphyxia were the major risk factors for cerebral palsy.

Lopes A et al studied and described that anomalies in the cranial ultrasound and in the electroencephalography were correlated with clinical evolution. They still are first line exams in the initial approach to underlying pathology.[7]Cranial ultrasound, EEG and neuroimaging were performed in selected patients in the present study according to clinical assessment and progression. The prognostic factors for long term neurodevelopmental outcome in the present study were mode of delivery, place of delivery, Apgar score at 5 minutes, resuscitation at birth, underlying etiology, neonatal status epilepticus, neuroimaging findings, and response to acute management. Painter MJ et al described that babies who had the highest seizure severity following treatment, abnormal imaging studies and those with epilepsy were more likely to have adverse outcomes[23]. Others studies showed that mortality was 12-22% while mortality in the present study was 12.5%[7,13,25].

CONCLUSIONS

Clonic seizures are commonest in neonates apart from infants and children who have GTCS. The most common etiology of seizures in neonates is birth asphyxia. Phenobarbitone is still the most commonly prescribed antiepileptic. Quick assessment, timely diagnosis and aggressive management according to the etiology are necessary to prevent the morbidity and mortality associated with neonatal seizures. Long term neurodevelopmental outcome is worse in patients with birth asphyxia especially with low Apgar score at 5 minutes. Normal delivery and birth asphyxia were the major risk factors for cerebral palsy.

RECOMMENDATIONS

Due to the limitations of this study, the following are recommended for future investigation: To increase sample size and extend period of investigation; to include patients admitted in other hospitals in our locality; and to conduct further investigation in all age groups.

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All truth passes through three stages.
First, it is ridiculed. Second,
it is violently opposed.
Third, it is accepted as being self-evident.

Arthur Schopenhauer (1788-1860)