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Study of Etiology, Onset and Clinical Manifestations of Neonatal Seizures in a Tertiary Care Centre

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Abstract

Background: *The most vulnerable period of life to develop seizures is the neonatal period. These events very often signify serious damage or malfunction of the immature developing central nervous system. Neonatal seizures may arise as a result of diverse etiologies and can have varied presentations.*

Aims and Objective: *Our study was aimed to find etiological factors, time of onset, clinical manifestations and various outcomes of neonatal seizures.*

Methods: *There were 110 neonates admitted in the NICU of a tertiary care centre in metropolitian city, with history of convulsions during the study period of 24 months from November 2016 to October 2018. Detailed antenatal history and baseline characteristics of convulsing neonate were recorded at admission. Clinical details of each seizure episode reported by the mother and subsequently observed by the resident doctors on duty were recorded. Venous blood was collected as soon as possible and blood glucose, total serum calcium levels, Na+, K+, Mg and P-levels were done immediately after baby had seizures and before instituting any treatment. Data was described as mean ± SE and %age. SPSS 22.0 and MS Excel software were used for data analysis.*

Results: *Hypoxic ischemic encephalopathy was the commonest etiology of neonatal seizures followed by neonatal meningitis. Majority of Hypoxic ischemic encephalopathy patients presented with seizures in the first 72 hrs. of life. Subtle seizures were the commonest seizure types encountered. Hypoglycaemia was the commonest biochemical abnormality in primary metabolic seizures. Hypocalcaemia was the next commonest abnormality and most common outcome was Residual neurological abnormality followed by Epilepsy.*

Conclusions: *Hypoxic ischemic encephalopathy was the commonest etiology with subtle seizures being the commonest clinical types encountered. Hypoglycaemia was the most frequent biochemical abnormality found and most common outcome was residual neurological abnormality.*

Introduction

Seizures are the most common and most important manifestation of neurologic dysfunction in neonates and carry a high risk for mortality and adverse long-term outcomes. 57.5 per 1000 neonates with birth weight <1.5 gm and 2.8 per 1000 neonates weight between 2.5 and 3.99 kg have seizures. The occurrence of neonatal seizures per se has been positively correlated with structural brain damage

and its consequent sequels at later stages in life. Seizures are a sign of an underlying cerebral pathology, the most common of which is Hypoxic-Ischaemic Encephalopathy (HIE) in term neonates (78%) followed by Septicaemia, Hypoglycaemia and Meningitis in order of frequency. The commonest type of seizures is subtle seizure (45.5%) followed by tonic, clonic, spasm and myoclonic seizures. Hypoxic-ischemia is considered the most common cause of neonatal seizures. Metabolic disorders and Meningitis are the second most common cause of neonatal seizures occurring in full term small for gestational age neonates. Intracranial hemorrhage is implicated in 10% to 15% of seizures. Hypomagnesaemia with serum <1.5 mg/dl can occasionally manifest with tetany and seizures at 2-4 weeks of age. Hyponatraemia as a result of fluid overload, renal compromise and SIADH (syndrome of inappropriate ADH secretion) can be a frequent complication of birth asphyxia and could complicate the management of seizures in this condition. Subtle seizures are the most frequent seizure type, which may consist of only horizontal deviation and or jerking of the eyes, repetitive blinking or fluttering of eyelids, drooling, suckling or other oro- buccal movements. Neonates with seizures are at risk of death, whereas survivors are at risk of neurological sequelae, developmental delay, later epilepsy and cognitive impairment. So, we need to initiate an early diagnostic workup to determine the causes. Early recognition and treatment of biochemical disturbances are essential for the optimal management and satisfactory outcome. There is a strong correlation of time of onset of neonatal seizures with the etiology and prognosis. For example, birth asphyxia usually presents in the first three days of life whereas meningitis usually presents after first week. If baby convulse within hours of delivery, it signifies poor prognosis and brain damage.

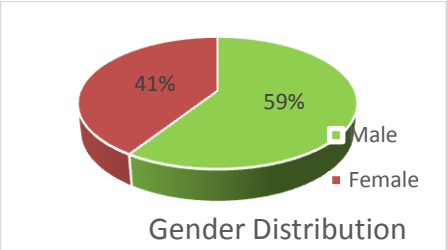
Materials and methods

This study of etiology, onset and clinical manifestations and outcome of neonatal seizures was conducted in the Neonatal Intensive Care Units (NICU) of a tertiary care centre in the metropolitian city over a period of 24 months. Proper history, clinical examination was performed on all the admitted neonates with seizures. The study population was selected according to inclusion criteria. The structured proforma included antenatal history, natal history, post natal history, family history, immunisation history, general and systemic examination, relevant laboratory findings. Proper maternal and neonatal histories were taken from reliable person, clinical examinations were done using aseptic precautions. Rectal/Axillary temperature was measured using clinical thermometer. Pupillary response was examined using a pen torch. Arterial and venous blood was drawn using aseptic precautions for required biochemical and haematological investigations. Lumbar puncture was done in all neonates with convulsions after taking proper consent. Multichannel non-invasive monitor was used to monitor heart rate, saturation of oxygen and carbon dioxide. Statistical analysis: Data was described as mean ± SE and %age. Software used for data analysis was SPSS 22.0 (statistical package for social sciences) and MS Excel. Complete Blood Count, continuous Electroencephalography was essential for the diagnosis of seizures in neonates due to their subtle clinical expression, non-specific neurological presentation and a high frequency of electro-clinical uncoupling in the neonatal period. Blood sugar, serum electrolytes such as sodium, potassium, serum calcium, magnesium and urea nitrogen level, Lumbar puncture, Metabolic workup, USG Skull, CT Brain, MRI Brain and genetic testing were done.

Results and observation

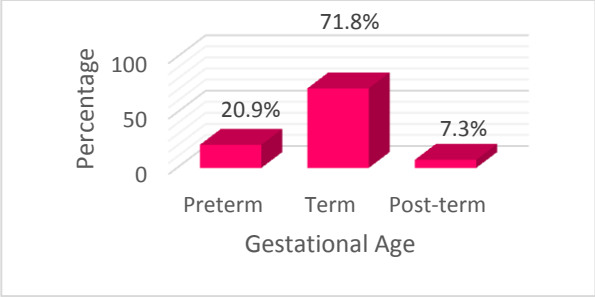
There were 110 neonates admitted in the NICU of a tertiary care centre in metropolitian city, with history of convulsions during the study period of 24 months from October 2016 to November 2018.

Graph 1: Showing Gender distribution of neonates included in this study



In this study, among 110 neonates with neonatal seizures, 64 neonates (59%) were male and 46 neonates (41%) were female with male to female ratio 1.4:1.

Graph 2: Showing Gestational Age of neonates included in this study



The distribution of gestational age of neonates included in this study are depicted in Graph 2 which showed that 79 neonates (71.8%) were full term appropriate for gestational age, 23 neonates (20.9%) were preterm, and 8 neonates (7.35%) were post term. Mean gestational age in this study was 37.2 weeks

Incidence of Birth asphyxia in relation to type of Liqour

In this study, 34 mothers (30.9%) had meconium stained liquor ,of which 22 mothers (20%) had thick meconium stained amniotic fluid and 12 mothers (10.9%) had thin meconium stained liquor and 76 mothers (69.1%) had clear amniotic fluid.

Day of onset and type of seizure

In this study, onset of seizures on first day of life was seen in 22 neonates (20%), seizures developed between 24 to 48 hrs of life in 38 neonates (34.5%). 34 neonates (30.9%) developed seizure between 3 days to 7 days of life and 16 neonates (14.5%) had first episode of seizures after 7 days. The first three days of life together constituted 54.5% (60 neonates) of neonatal seizure. 99 neonates (90%) had one of the 4 classically described neonatal seizures. Among these, 45 neonates (40.9%) had subtle seizures, 32 neonates (29.1%) had generalized tonic seizures, 13 neonates (11.8%) had multifocal clonic seizures and 9 neonates (8.2%) had focal clonic seizures. 11 neonates (10%) had mixed type of seizures, among these 6 neonates (5.5%) had subtle with generalized tonic seizures and 5 neonates (4.5%) had subtle with clonic seizures.

Etiology of neonatal seizure

In this study, 43 neonates (39%) had Birth asphyxia. 27 neonates (24.5%) had infectious etiology, in which most common cause was Meninigitis in 19 neonates (19/27-70.3%) followed by 5 neonates (18.5%) with Encephalitis, 2 neonates (7.4%) had Cerebral Malaria .13 neonates (12%) had Hypoglycemia.11 neonates (10%) were diagnosed as a case of Hypocalcaemic seizures. 4 neonates (3.6%) had Genetic cause for neonatal seizures followed by 3 neonates (2.7%) with Intraventricular Hemorrhage and Inborn Error of Metabolism. Hypoxic ischaemic encephalopathy was the commonest cause of neonatal seizures in this study.

Final outcome of neonatal seizures

Final neurodevelopmental outcome of neonatal seizures showed that 51 neonates (46.3%) were normal without any neurological sequelae. 30 neonates (27.3%) developed residual neurological abnormality, most common cause being Hypoxic Iscahemic Encephalopathy. 11 neonates (10%) developed Epilepsy mainly due to genetic causes.18 neonates (16.4%) expired due to Birth asphyxia, intraventricular hemorrhage, metabolic causes, hence morbidity rate was 37.2% and mortality rate was 16.4%.

Association of Etiology and day of onset of seizure

In this study, the onset of seizures on first day was seen in 22 neonates (20%), 17 of them (17/22-77.2%) were due to Birth asphyxia and 3 were

(13.6%) due to infectious causes mainly meningitis. 38 neonates (34.5%) developed seizures between second and third day, 25 of them (65.7%) were due to Birth asphyxia, 5 were (13.1%) due to infectious causes and 4 were (10.5%) due to hypoglycaemia. Among 4 neonates who had genetic disorders, 2 neonates (2/22-9%) developed seizures on first day, 2 neonates (2/38-5.2%) developed seizures on second and third day of life along with 2 neonates (5.2%) due to metabolic etiology. Chi square test for onset of seizures on first three days with etiology =104.489 with p value < 0.001 which was statistically very highly significant for onset of seizures on first three days of life with Birth asphyxia.

Correlation of Etiology with type of neonatal seizures

In the present study, out of 43 neonates (39%) with Hypoxic Ischaemic Encephalopathy, 24 neonates (55.8%) had subtle seizures, followed by GTS and subtle with GTS in 6 neonates (13.9%) , subtle with clonic seizures in 4 neonates (9.3%) and MFC (multifocal clonic) seizures in 2 neonates (4.6%). In neonates with meningitis (19 neonates 70.3%), 11 neonates (11/19-57.8%) had GTS and 8 neonates (8/19-42.1%) developed subtle seizures. In neonates with hypoglycaemic seizures, 6 neonates (6/13-46.1%) had GTS followed by subtle seizures in 3 neonates (3/13-23.6%). Chi square test for neonates with GTS, Subtle seizures and clonic seizures with etiology = 64.624 p=0.002 (highly significant). In this study there was a strong correlation between types of neonatal seizures with the etiology ($p<0.05$). Most common type of seizures in Birth Asphyxia was Subtle followed by Generalised Tonic Seizures.

Association of Etiology and Gestational Age of neonates

In the present study, among 79 term neonates (71.8%), 32 neonates (32/79-40.5%) had Birth asphyxia, 11 neonates (11/79-13.9%) had meningitis, 9 neonates (11.4%) had hypoglycaemia, 8 neonates (10.1%) had hypocalcaemia, 4 neonates (5%) had electrolytes imbalance, 2 neonates (2.5%) had genetic disorder, 3 neonates (3.8%) had metabolic disease. Out of 23 preterm neonates (20.9%), 8 neonates (8/23-34.7%) had meningitis, 4 neonates (17.3%) had hypoglycaemia, 3 neonates (13%) had asphyxia, 3 neonates (13%) had hypocalcaemia, 2 neonates (8.7%) had IVH and 2 neonates (8.7%) had genetic etiology. Out of 8 post-term neonates (8/110-7.2%), all neonates had Birth asphyxia. Chi square test for gestational age of neonates with etiology = 24.604, P = 0.039 (significant). Hence in this study, Birth asphyxia was most common in full term and post term neonates while hypoglycaemia was common in preterm neonates.

Association of Etiology of neonatal seizures and Outcome

In this study, out of 43 neonates (43/110-39%) with Birth asphyxia, 21 neonates (21/43-48.8%) developed residual neurological abnormality, 4 neonates (9.3%) had epilepsy, 12 neonates (27.9%) were normal with no neurodevelopmental sequelae and 6 neonates (14%) died due to respiratory failure. Out of 27 neonates (27/110-24.5%) with infectious etiology, only 1 neonate (3.7%) died because of refractory septicaemic shock, 18 neonates (66.7%) were normal. 13 neonates (11.8%) had hypoglycaemic seizures, of which 3 neonates (23.1%) developed residual neurological abnormality, 3 neonates (23.1%) died due to septicaemia. Hypocalcaemic seizures were found in 11 neonates (10%) of which 1 neonate (9.1%) developed epilepsy with abnormal EEG report, rest all were normally. 6 neonates (5.4%) had electrolytes imbalance, most common being hyponatraemia and hypernatraemia due to SIADH and severe dehydration. 2 neonates (2/6-33.3%) expired due to severe acidosis and CNS infection. 3 neonates (2.7%) had metabolic disorders as a cause of seizures, all died due to respiratory and liver pathology. 3 neonates (2.7%) had IVH and all neonates died due to respiratory failure and septicaemia. 4 neonates (3.6%) had genetic disorders as a cause of seizures and all neonates

developed epilepsy. Chi sqare test of neonatal seizures etiology and neurodevelopmental outcome= 98.052 p=<0.001 (very highly significant). Hence from this study, there was a strong correlation between etiology of neonatal seizures and neurodevelopmental outcome.

Discussion

Neonatal seizures had slight predominance of male to female neonates. Male to Female ratio was 1.4:1. Seizures due to Birth asphyxia (39%) was seen more commonly in term appropriate for gestational age and all post term neonates and associated with perinatal factors like meconium stained liquor whereas seizures due to Hypoglycaemia (11.8%) was more common in low birth weight neonates. Most of neonatal seizures occured in the first week of life (85.4%), more so within first 3 days of life (54.5%). Highest number was seen on second day of life. The most common type of seizures was Subtle seizures (40.9%), followed by generalized tonic (29.1%), multifocal clonic (11.8%), focal clonic type (8.2%) and mixed type of seizures (10%). The commonest cause of neonatal seizures was Hypoxic Ischaemic Encephalopathy (39%) followed by Neonatal Meningitis (17.3%). Seizures due to Birth asphyxia had onset within first 3 days of life (97.6%) more so during second day (58.1%) with statistically significant correlation between etiology and onset of seizures (p<0.001). Majority of Hypoglycaemic seizures occured during, third and fourth day (92.3%). Seizures due to neonatal meningitis had onset at the end of first week and early second week. Hypocalcaemic seizures had 2 peaks, one on second day and the other after first week of life. Neonatal meningitis in this study was the second most common cause of seizures (17.2%). Organisms causing meningitis were mostly MRCONS and Klebsiella pneumonie which is community acquired or nosocomial acquired. This could be prevented by proper hand washing technique and hygienic delivery. Hypoglycaemia was the third most common cause of neonatal seizures (11.8%) and had adverse effect on brain therefore early detection and treatment of hypoglycaemia prevent brain injury and poor neurodevelopmental outcome. Most common neurological sequel was Residual neurological abnormality (27.3%) followed by Epilepsy (10%). Birth asphyxia was mainly responsible for development of Residual neurological abnormality. Mortality in this study was 16.4% (18/110) and Birth asphyxia was the leading cause of death. Morbidity rate was 37.2% (41/110). Birth asphyxia had poor neurodevelopmental outcome in the form of residual neurological abnormality (most common) and epilepsy. All patients with genetic causes developed epilepsy. Early detection of etiology of neonatal seizures is helpful with respect to prognosis and treatment. Subtle seizures were the commonest type of clinical seizures, which was difficult to identify, therefore careful observation of at risk newborns is necessary. The occurrence of seizures may be the first indication of neurological disorder and the time of onset of seizures has a correlation with the etiology of seizures and prognosis.

Conclusion and Recommendations

The most common etiology of neonatal seizures is Hypoxic-Ischemic Encephalopathy due to Birth asphyxia (39%) followed by Metabolic disorders (27.2%), CNS infection (24.5%) commonest being Neonatal Meningitis and Intracranial Hemorrhage (2.7%). Perinatal complications like MSAF, PIH, prolonged second stage of labour and unsafe home deliveries are frequently associated with HIE. Hence these can be prevented by proper antenatal and perinatal care to the mother. Most of the seizures occur in first 3 days of life and mainly due to Birth asphyxia (42/43-97.6%), hence the time of onset of neonatal seizures is significantly associated with the etiology. Subtle seizures are commonest type (40.9%) of clinical seizure and seen mainly in neonates with Birth asphyxia. Most common neurodevelopmental abnormality is Residual neurological abnormality (27.3%) followed by Epilepsy (10%) and most common etiology being Birth asphyxia. Mortality rate is 16.4% and Morbidity rate is 37.2%. Hence from outcome, it is

found that mortality rate has decreased significantly due to improved neonatal intensive care in NICU of a tertiary care centre but morbidity is same. Most of the neonatal seizures are associated with perinatal complications, continued advances in perinatal and neonatal medicine may reduce seizure incidence in the future and prevent the neurologic, cognitive and epileptic consequences of neonatal seizures.

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