

Etiological Profile and Associated Demographic, Perinatal and Clinical Variables of Neonatal Seizure among Neonates Admitted with Seizure in a Tertiary Care Hospital, Jaipur

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Abstract:

Introduction: This study was conducted to determine proportion of various etiological factors of newborns having seizures admitted in SNCU and associated demographic, perinatal and clinical factors.

Methodology: This Retrospective hospital record based study was conducted at Special Newborn Care Unit (SNCU), Department of Pediatrics, Govt. R.D.B.P Jaipuria Hospital Jaipur, among neonates admitted in SNCU with clinical diagnosis of Neonatal seizures from 1st January, 2021 to 31st July, 2021. Sample size was calculated as 100 taking proportion of HIE as an etiology of neonatal seizures 44.4%. Medical records of the hospital were assessed in a semi-structured, pre-tested proforma. All statistical analysis was done using Epi info version 7.2.1.0 statistical software.

Result: Most of the neonates with seizure were males (63%), full term (73%). 61 % had birth weight >2.5 kg and 12 % were IUGR (SGA) while 27% had preterm birth. Meconium-stained liquor was found in 39% neonates. In history of maternal illness, PIH was most common (16%). Most commonly, seizures occurred in first 24 hrs (43%) followed by day 2 (25%) and day 3-7 (25%) and the least after day 7 (7%). Subtle seizure was the most common type of seizure and Hypoxic ischemic encephalopathy was the most common etiology of seizures in neonates (62%), followed by hypoglycemia (22%), Meningitis (8%), IVH (4%), Hypocalcemia (2%) and brain malformation (2%). Most common type of seizures due to HIE was subtle seizure (83.9%) followed by tonic seizures (11.3%). HIE mostly caused seizures on Day 1 (61.3%) followed by day 2 (17.7%). Etiology was significantly associated with type and time of onset of seizure.

Conclusion: Hypoxic ischemic encephalopathy was the most common etiology and Subtle seizure was the most common type of seizure. Etiology is significantly associated with type and time of onset of seizure.

Keywords: seizures, perinatal, hypoxic ischemic encephalopathy.

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Introduction

The first month of life is one of the highest risk periods for seizures. This is the most common manifestation of neurological conditions in the neonates as immature brain is more prone to seizures than the mature brain. A seizure is defined as paroxysmal alteration in neurological function.

This could be behavioral, sensory, motor, and autonomic. [1] The incidence of Neonatal Seizure is 2.8 per 1000 in infants with birth weights of more than 2500g. [2] Seizures in neonates are different from those seen in older children. The differences are perhaps due to the neuroanatomic and neurophysiologic developmental status of the newborn infant.

In the neonatal brain glial proliferation, neuronal migration, the establishment of axonal deposition, dendritic contacts, and myelin deposition are incomplete. For these reasons, clinical presentation differs. [3] Neonatal seizures may be the initial and sometimes the only, manifestation of neurological disorder in the newborn child.

In the newborn the behavioral features of seizures may be very subtle, in some cases confined to autonomic and subtle motor phenomena. Clinical seizure types may be categorized broadly into four groups: subtle seizures, clonic (focal, multifocal) seizures, tonic seizures, and myoclonic seizures

(Adapted from Volpe, Volpe Classification). [4] In many cases, more than one type of seizure occurs in a newborn over time. The etiology behind the abnormal central nervous system (CNS) electrical discharge may be Intracranial (eg - meningitis, ischemic stroke, encephalitis, intracranial hemorrhage, tumor, malformation) or Systemic (eg hypoxia-ischemia, hypoglycemia, hypocalcemia, hyponatremia, other disorders of metabolism). Hypoxic-ischemic encephalopathy (HIE) is the commonest cause of NS, occurring in approximately 1 to 2 per 1000 live births.⁵ Other causes of Neonatal Seizure included Focal ischemic injury, Intracranial hemorrhage, Central nervous system infections, Metabolic disturbances, Maternal substance abuse, Inborn errors of metabolism, Brain malformation cerebral digenesis, Epileptic syndromes. Although in about 10% of cases, no cause for NS may be identified. [6]

Neonatal seizures may be difficult to differentiate from either normal Behaviours or abnormal movements of non-epileptic origin and delayed treatment may lead to brain damage. The time of onset of seizure also has association with the etiology and prognosis. Therefore, the present study was aimed to determine the proportion of common etiologies of neonatal seizures among newborns who has been admitted with seizures at the SNCU of a government district hospital of Jaipur and associated demographic, perinatal and clinical variables.

Materials and Methods

This Retrospective hospital record based study was conducted at Special Newborn Care Unit (SNCU), Department of Pediatrics, Govt. R.D.B.P Jaipuria Hospital (Attached with RUHS College of Medical Sciences), Jaipur, Rajasthan among neonates admitted in SNCU with clinical diagnosis of Neonatal seizures.

Sample size was calculated at 95% confidence interval and 10% relative allowable error using the formula for sample size for estimation of a single sample proportion

Where,

$(Z_{1-\alpha/2})^2 =$ Standard normal deviate for 95% confidence interval (taken as 1.96)

P = Expected proportion of HIE as an etiology of neonatal seizures (taken as 44.4% as reported by Veena Anand et al) [7]

E = Relative allowable error (taken as 10% of P)

Sample size was calculated to be a minimum of 95 subjects, which was enhanced and round to 100 subjects of neonatal seizures. These 100 subjects were recruited from all the neonates having clinically diagnosed seizures. Selection of subjects was done based on following criteria for inclusion and exclu-

sion.

Inclusion criteria:

- Neonates (age up to 28 days), irrespective of gender.
- In-born neonates of the hospital and out-born neonates who were transferred to the hospital were included.

Exclusion Criteria:

- A neonate for who complete data was not available from records.
- Neonates who by virtue of their parents left against medical advice (LAMA)/ were shifted to other hospitals or those who expired before specific etiology.

After obtaining ethical clearance from Institutional Ethical Committee (IEC) and medical superintendent's permission to assess hospital records, the study was carried forward from 1st January, 2021 to 31st July, 2021 for 7 months. Medical records of the hospital were assessed in a semi-structured, pre-tested proforma maintaining anonymity of the study participants.

Relevant demographic details, significant maternal (antenatal) history, perinatal history, need for advanced resuscitation etc. were thoroughly evaluated. Apgar score was considered as suggestive of birth asphyxia as ≤ 6 at 5 mins.⁸ Gestational age assessment and Physical examination were done according to New Ballard Score.⁹ History characterizing seizure namely type, time of onset, duration, presence of status epilepticus etc. Volpe classification⁴ was used to determine the type of seizure.

Values of Routine chemistries, including blood sugar, sepsis screen including total leucocyte count, absolute neutrophil count, C-reactive protein, micro ESR, serum electrolytes such as sodium, calcium, magnesium were recorded.

Lumbar puncture, arterial blood gas analysis, TORCH screen and screen for inborn errors of metabolism were done wherever indicated. The etiology of seizures and final diagnosis were established after thorough clinical and laboratory evaluation. Neurological assessment and cranial ultrasound of the subject were done when they were fit for discharge.

All data emanating from this study was entered into proforma and then coded into a MS Excel sheet, cleaned and verified. Categorical variables were summarized as frequency and proportion and were analyzed using the Chi- square test.

Both descriptive and analytical statistics was used for analysis of data. All statistical analysis was done using Epi info version 7.2.1.0 statistical software. Qualitative Data was expressed in proportions and

also summarized using appropriate graph and charts while Mean and standard deviation were calculated for quantitative data. A p-value < 0.05 was considered as statistically significant.

Results

A total of 100 participants were included in the study. Most of the neonates with seizure included in the study were males (63%), while only 37% were females. Majority of the neonates (73%) were full

term while 27% had preterm birth. Majority of the neonates (61%) had normal birth weight (≥ 2.5 Kg), while 39% were low birth weight (< 2.5 Kg).

Most of the neonates (88%) were appropriate for gestational age, while only 12% were small for gestational age.

Most neonates were delivered by normal vaginal delivery (73%), while 25% had LSCS and 2% were delivered by assisted vaginal delivery. [Table-1]

Table 1: Distribution of Subjects according to Demographic Variables

| Characteristics | Subgroup | N | % |
|---------------------|---------------|----|----|
| Gender | Female | 37 | 37 |
| | Male | 63 | 63 |
| Gestational age | Full Term | 73 | 73 |
| | Pre-Term | 27 | 27 |
| Birth weight | <2.5 Kg | 39 | 39 |
| | ≥ 2.5 Kg | 61 | 61 |
| Intrauterine growth | AGA | 88 | 88 |
| | SGA(IUGR) | 12 | 12 |
| Mode of delivery | NVD | 73 | 73 |
| | AVD | 2 | 2 |
| | LSCS | 25 | 25 |

Meconium-stained liquor was found in 39% neonates. In history of maternal illness, PIH was most common (16%), followed by PROM>12 hours (15%) and APH (12%). Fever within 7 days seen in 10 subjects. Most (64%) of the neonates with seizures had APGAR score ≤ 6 at 1 minute and an APGAR score of ≤ 6 at 5 minutes (62%). Most (62%) neonates needed advanced resuscitation at birth. [Table-2]

Table 2: Distribution of Subjects according to Perinatal Variables

| Characteristics | Subgroup | N | % |
|--|---------------------|----|----|
| Meconium-stained liquor | No | 61 | 61 |
| | Yes | 39 | 39 |
| Maternal illness | Fever within 7 days | 10 | 10 |
| | PIH | 16 | 16 |
| | PROM >12 hours | 15 | 15 |
| | APH | 12 | 12 |
| APGAR score at 1 min | ≤ 6 | 64 | 64 |
| | > 6 | 36 | 36 |
| Need for advanced resuscitation at birth | Yes | 62 | 62 |
| | No | 38 | 38 |
| APGAR score at 5 min | ≤ 6 | 62 | 62 |
| | > 6 | 38 | 38 |

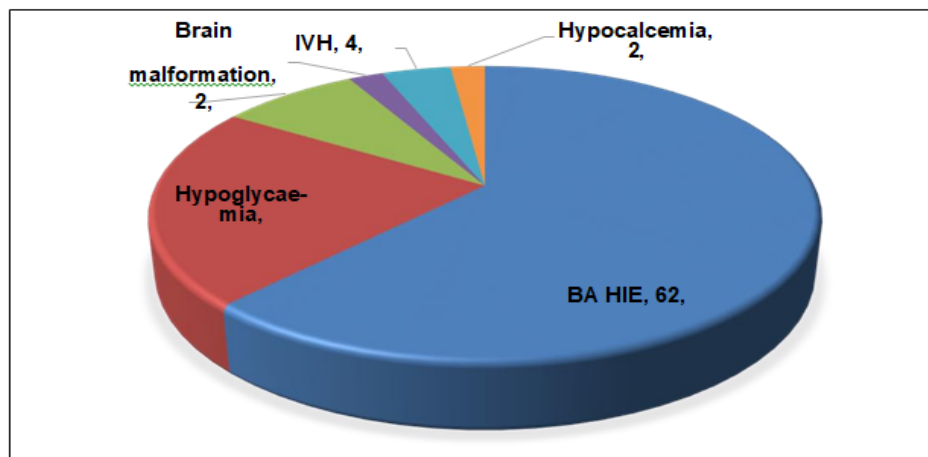
Subtle seizure was the most common type of seizure (71%) followed by Tonic seizure (11%), Focal Clonic (9%), Multi focal Clonic (7%) and myoclonic seizures were seen in only 2% study participants. Most commonly, seizures occurred in first 24 hrs (43%) followed by day 2 (25%) and day 3-7 (25%) and the least after day 7 (7%). [Table-3]

Table 3: Distribution according to Type and time of onset of Seizures

| Clinical features | Total (n) | Total (%) |
|----------------------------------|-----------|-----------|
| Type of seizures | | |
| Subtle | 71 | 71% |
| Focal Clonic | 9 | 9% |
| Multi focal clonic | 7 | 7% |
| Tonic | 11 | 11% |
| Myoclonic | 2 | 2% |
| Time of onset of seizures | | |

| | | |
|---------------|------------|-------------|
| Day 1 | 43 | 43% |
| Day 2 | 25 | 25% |
| Day3 – 7 Days | 25 | 25% |
| > 7 Days | 7 | 7% |
| Total | 100 | 100% |

Hypoxic ischemic encephalopathy was the most common etiology of seizures in neonates (62%), followed by hypoglycemia (22%). Meningitis was the etiology in 8% neonates. Other rare etiologies include IVH (4%), Hypocalcemia (2%) and brain malformation (2%). [Graph-1]



Graph 1: Distribution of study subjects according to etiology of seizures

Most common type of seizures due to HIE was subtle seizure (83.9%) followed by tonic seizures (11.3%).

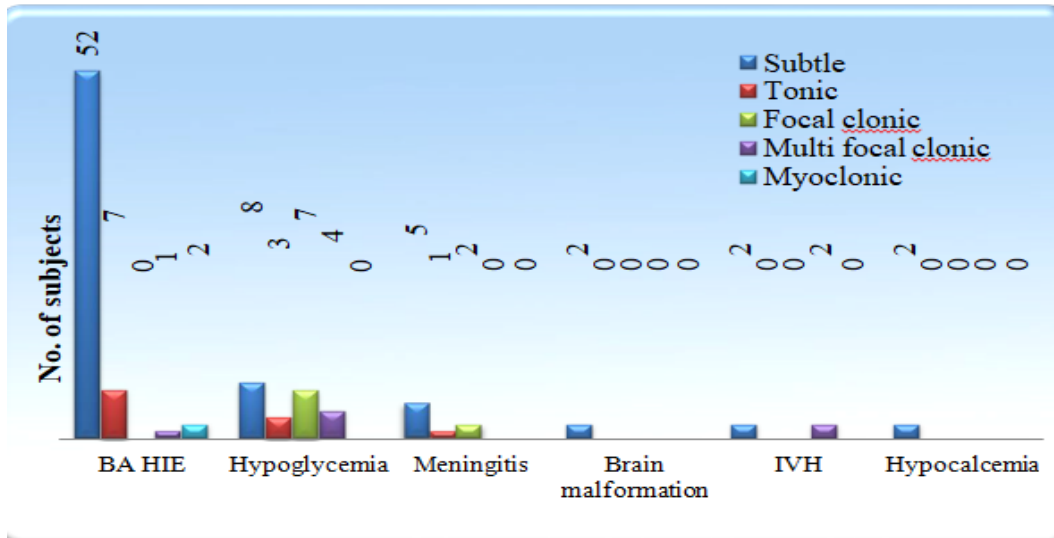
In hypoglycemia subtle seizure (36.4%) was more common followed by focal clonic seizures (31.8%), multifocal clonic (18.2%) and tonic seizures (13.6%). In Meningitis subtle seizures (62.5%) were most common, followed by focal clonic (25%)

and tonic seizures (12.5%). Brain malformation caused subtle seizures in 2 cases. IVH caused subtle seizures in 2 (50%) and multifocal clonic seizures in 2 (50%) cases.

Both the hypocalcemia cases had subtle seizures (100%). This difference in type of seizures in different etiology was found to be statistically significant ($p < 0.001$). [Table-4, Graph-2]

Table 4: Association of Type of seizures with etiology

| Etiology | Subtle (%) | Tonic (%) | Focal clonic (%) | Multi focal Clonic (%) | Myoclonic (%) | P value |
|--------------------------|------------|-----------|------------------|------------------------|---------------|---|
| Type of seizures | | | | | | |
| BA HIE (n=62) | 52 (83.9) | 7(11.3) | 0 (0) | 1 (1.6) | 2 (3.2) | Chi- square = 47.44 2; P < 0.001 (S) |
| Hypoglycemia (n=22) | 8 (36.4) | 3(13.6) | 7 (31.8) | 4(18.2) | 0(0) | |
| Meningitis (n=8) | 5(62.5) | 1(12.5) | 2(25) | 0(0) | 0(0) | |
| Brain malformation (n=2) | 2(100) | 0(0) | 0(0) | 0(0) | 0(0) | |
| IVH (n=4) | 2(50) | 0(0) | 0(0) | 2(50) | 0(0) | |
| Hypocalcemia (n=2) | 2(100) | 0(0) | 0(0) | 0(0) | 0(0) | |



Graph 2: Association of Type of seizures with etiology

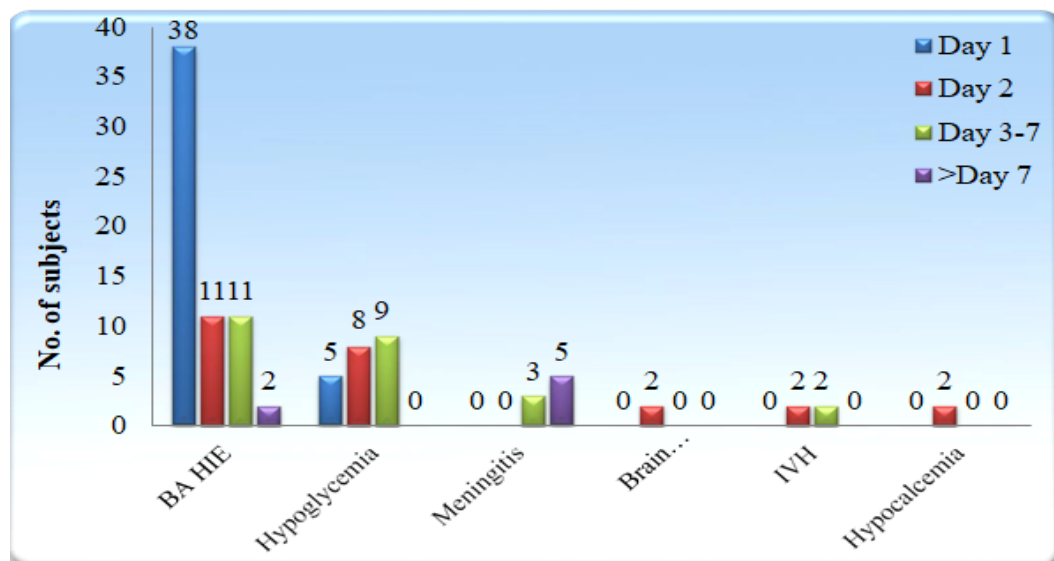
HIE mostly caused seizures on Day 1 (61.3%) followed by day 2 (17.7%) and Day 3-7 (17.7%) and rarely after day 7. Hypoglycemia however caused seizures mostly on day 3-7 (40.9%) and Day 2 (36.3%) followed by day 1 (22.7%). Meningitis was mostly responsible for seizures after day 7 (62.5%) and did not cause seizures within 24 hours. IVH caused seizures on day 2 (50%) and day 3-7

(50%). Brain malformation and hypocalcemia caused seizures only on day 2, this could however be non-representative as only 2 cases each were seen of these etiologies.

This difference in time of onset of seizures in different etiology was found to be statistically significant ($p < 0.001$). [Table-5, Graph-3]

Table 5: Association of Time of onset of seizures with etiology

| Etiology | Day 1 (%) | Day 2 (%) | Day 3-7 (%) | >Day 7 (%) | P value |
|---------------------------------|--------------|--------------|-------------|------------|--------------------------------------|
| Time of onset of seizure | | | | | |
| BA HIE(n=62) | 38 (61.3) | 11 (17.7) | 11(17.7) | 2(3.2) | Chi- square = 48.253 ; P < 0.001 (S) |
| Hypoglycemia (n=22) | 5 (22.7) | 8 (36.3) | 9(40.9) | 0(0) | |
| Meningitis (n=8) | 0 (0) | 0(0) | 3(37.5) | 5(62.5) | |
| Brain malformation(n=2) | 0 (0) | 2(100) | 0(0) | 0(0) | |
| IVH (n=4) | 0(0) | 2(50) | 2(50) | 0(0) | |
| Hypocalcemia (n=2) | 0(0) | 2(100) | 0(0) | 0(0) | |



Graph-3: Association of Time of onset of seizures with etiology

Discussion

The present study was an attempt to add more evidence to existing research in the field of knowledge associated with neonatal seizures. In our study most of the neonates with seizure included were males (63%), while only 37% were females similar to the study of Nair BK et al [10] (65.33% males and 34.66% females), Mitesh Chawda et al [11] (56.67% males and 43.33% females), Kumar R et al [12] (65.4% males and 34.6% females) and Venkatesh G et al [13] (62.8% males and 37.2% females). Seizures were observed more commonly in male babies (44 babies) than female (16 babies) in study of Rastogi S et al [14]. Majority of the neonates (73%) were full term in our study in agreement with study of Nair BK et al [10] (69.33%), Rastogi S et al [14] (>80%) and Srinivasa Rao et al [15] found that incidence was more common in full term neonates 74(68.5%). Majority of the neonates (61%) had normal birth weight (≥ 2.5 Kg), in agreement with study of Mitesh Chawda et al [11] where 68.67% were of more than 2.5 kg birth weight. Most neonates were delivered by normal vaginal delivery (73%), while 25% had LSCS and 2% were delivered by assisted vaginal delivery. Vijay Agrawal et al [16] found that Majority of cases of neonatal seizures are delivered by Normal vaginal 86 (86%) and rest are delivered by caesarean 14(14%).

Meconium-stained liquor was found in 39% neonates. In history of maternal illness, PIH was most common (16%), followed by PROM>12 hours (15%) and APH (12%). Fever within 7 days seen in 10 subjects. Most (64%) of the neonates with seizures had APGAR score ≤ 6 at 1 minute and an APGAR score of ≤ 6 at 5 minutes (62%). Most (62%) neonates needed advanced resuscitation at birth. These findings can be explained by the fact that majority of seizures in our study are caused by moderate to severe birth asphyxia associated HIE.

Subtle seizure was the most common type of seizure (71%) followed by Tonic seizure (11%), Focal Clonic (9%), Multi focal Clonic (7%) and myoclonic seizures were seen in only 2% study participants. Subtle seizure was the most common type of neonatal seizure seen in about 57% cases, followed by tonic seizures (31.6%) in study of Rastogi S et al. [14] In study of Mitesh Chawda et al [11] Subtle type of seizures was the most common type (54%) followed by Tonic type (25.33%) and clonic type of seizures (20%) cases. Myoclonic type accounted for only 1 case (0.67%)

Most commonly, seizures occurred in first 24 hrs (43%) similar to the study of Nair BK et al [10] (53.33%) and Rastogi S et al [14] (35%). While in study of Mitesh Chawda et al [11] maximum subjects (36.67%) had seizure onset on day of life 2 to 3, followed by 34% cases had seizures onset on first

day of life. 26% cases had seizure onset on day of life 4 to 7 and 3.33% cases had onset of seizures after 7th day of life.

In our study birth asphyxia associated hypoxic ischemic encephalopathy (BA HIE) was the most common etiology of seizures in neonates (62%) which can be attributed to the quality of antenatal care of mother and fetus among lower socioeconomic strata of society and level of perinatal and postnatal care at resource constrained setup like ours, followed by hypoglycemia (22%). Meningitis was the etiology in 8% neonates. Other rare etiologies include IVH (4%), Hypocalcemia (2%) and brain malformation (2%). Nair BK et al [10] found that most common cause of seizure among preterm and term is HIE. In study of Mitesh Chawda et al [11] the most common cause of neonatal seizures was Birth asphyxia (42.67%), followed by metabolic cause (38%), Meningitis (8.67%), and (2.67%) cases of cerebrovascular, hypoxia and unknown cause each. Shah GS et al (2008) [35] observed that Birth asphyxia (44%), the most common cause observed followed by meningitis and septicemia (22%). Among metabolic abnormalities hypoglycemia was found in 20 (22%) and hypocalcaemia in 10 (11%). Veena Anand et al [7] observed that Hypoxic ischemic encephalopathy (HIE) and sepsis constituted the most common etiologies. Vijay Agrawal et al [16] found most common cause of neonatal seizure as birth asphyxia (73%) second common cause is pyomeningitis and third common cause is hypoglycemia. Sepsis was the most common cause of neonatal seizures (64.9%), followed by HIE (48.3%) in study of Rastogi S et al. [14]

Most common type of seizures due to HIE was subtle seizure (83.9%) followed by tonic seizures (11.3%) similar to the study of Rastogi S et al [14]. Shah GS et al [17] and Amar et al [18] in their studies also observed that in birth asphyxia, the most common type of seizure subtle seizures (50% and 31.9% respectively) followed by focal clonic 25% and 25.5% respectively). HIE mostly caused seizures on Day 1 (61.3%) followed by day 2 (17.7%) and Day 3-7 (17.7%) and rarely after day 7. Bari ANA et al [19] found that the majority of seizures due to birth asphyxia were observed in first 48 hours life (early onset) while in infection, seizures were observed after 7 days of life (late onset). Hypoglycemia however caused seizures mostly on day 3-7 (40.9%) and Day 2 (36.3%) followed by day 1 (22.7%). Amar et al [18] also found that hypoglycemia was more commonly seen after 3 days.

Conclusion & Recommendations

Etiology of neonatal seizures can vary geographically depending upon population characteristics and level of health care. Hypoxic ischemic encephalopathy was the most common etiology of seizures in neonates in this study. Other etiologies included

hypoglycemia, Meningitis, IVH, Hypocalcemia and brain malformation. Scrutiny of factors like Pre term birth, Low birth weight, need for advanced resuscitation at birth, one minute APGAR score ≤ 6 , 5 minute APGAR score ≤ 6 , seizure onset within 24 hours of birth, status epilepticus, severe findings on neuro examination or on cranial imaging, can help in early identification of neonates at risk adverse neuro-developmental outcome and initiate timely and individualized intervention for these neonates. In our setup perinatal asphyxia was much more common as compared to other resource abundant setup hence results pertaining to study population are reflective of perinatal asphyxia. It is recommended that the researchers from the same region take the study forward in an analytical design to find out the temporal sequence and establish incidence rates for various etiologies of neonatal seizures.

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