ORIGINAL ARTICLE

AETIOLOGY AND TYPES OF NEONATAL SEIZURES PRESENTING AT AYUB TEACHING HOSPITAL ABBOTTABAD

Shahzad Najeeb, Azhar Munir Qureshi, Anis-ur-Rehman, Fayaz Ahmad, Sher Shah, Asfand Yar Khan*, Tahir Saeed Siddiqui

Paediatric Department of Ayub Teaching Hospital Abbottabad, *Army Medical College Rawalpindi, Pakistan

Background: Neonatal seizures (NS) affect approximately 1% of neonates. Clonic, tonic, myoclonic and subtle seizures are the common types. Birth asphyxia, sepsis, metabolic derangements, intracranial bleed, kernicterus, tetanus and 5th day fits are the common aetiologies. This study was planned to evaluate the types and causes of neonatal seizures. **Methods:** It was a descriptive case series conducted at Ayub Teaching Hospital, Abbottabad from 12th December 2006 to 25th September 2007 on neonates having seizures. Serum chemistry, blood counts, cerebrospinal fluid examination and cranial ultrasound were done in all patients. Blood culture, renal and liver function tests, computerised tomography scan, metabolic and septic screening was done in selected patients. Descriptive statistics were applied for analysis. **Results:** Tonic clonic seizure was the commonest type (28%) followed by multi-focal clonic, and focal tonic seizures (25% each). Birth asphyxia was found to be the main aetiology (46%). **Conclusion:** Tonic clonic seizure was the commonest type and birth asphyxia the main aetiology identified in the majority of neonatal seizures.

Keywords: Neonatal seizures, Aetiology, Seizures, Epilepsy, Neonates

INTRODUCTION

Seizures are more common in the neonatal period than in any other stage of life affecting approximately 1% of all neonates.[1] Neonatal seizures is defined as a paroxysmal phenomenon, required to have at least one of the following clinical manifestations: changes in behaviour, stereotyped or periodic motor activities or autonomic dysfunctions. However, in clinical practice at the paediatric or neonatal intensive care units (ICU), in developing countries where synchronised video-EEG monitoring is practically non-existent, clinical observation becomes the key to the diagnosis.[2]

Occurrence of seizures indicates dysfunction of the central nervous system. Determination of aetiology is critical, both for treatment and disease prognosis.[3] Neonatal seizures are of four main categories: tonic, clonic, myoclonic and subtle.[4] Birth asphyxia is the commonest cause of neonatal seizures[3] while other causes include septicaemia with or without CNS infection, transient metabolic disorder and intracranial bleed.[5] Hypocalcaemia is the commonest metabolic disorder followed by hypoglycaemia.[6] Brain malformation, hydrocephalus[5], inborn errors of metabolism including urea cycles defects, organic academia, mitochondrial abnormalities and pyridoxine dependency[6], kernicterus, lignocaine toxicity and 5th days fit are less common causes[5]. Overall 10–50% of patients die and 50% develop long term complications like epilepsy, cerebral palsy and mental retradation.[7] Outcome is predicted by the underlying aetiology.[8] Patients with hypoxic ischemic encephalopathy (HIE), intra-ventricular haemorrhage and structural brain malformation have the worst prognosis[8,9], while those with transient metabolic abnormalities and benign idiopathic or familial aetiologies have the best prognosis[9]. Aetiology of neonatal seizures is identified in 99% of cases and is rarely idiopathic.[5]

The present study was planned to evaluate the different types and causes of neonatal seizures in our setup so as to formulate an effective strategy for their management.

PATIENTS AND METHODS

After an informed written consent from parents/ attendants, a total of 100 neonates of either gender admitted in neonatal unit through Paediatrics OPD, Labour Room, and Emergency Room who presented with seizures or developed seizures in hospital, were included. Full-term neonates who developed fits within 28 days and preterm neonates up to 44 weeks of gestational age were included in the study. Gestational age was confirmed from parents by the last menstrual period (LMP), obstetrical ultrasonography or from clinical assessment (New Ballard Score).[10] Approval of the ethical committee was obtained.

Seizures were defined on the basis of clinical findings characteristic of each category.[11] Epileptic movements were differentiated from non-epileptic movements.[12]

Detailed history and examination was carried out. Perinatal history of birth asphyxia[13] was obtained, and delivery details were recorded. Family history of neonatal fits, deaths, jaundice and exchange transfusion was asked in detail. Feeding history was documented. Complete general and systemic physical examination was performed, and detailed neurological and eye examination including fundoscopy was carried out.

Investigations carried out were blood glucose, serum calcium, serum electrolytes, and complete blood count with peripheral film and Cerebrospinal fluid (CSF) for any evidence of infection. Cranial ultrasound was done to find out any intraventricular haemorrhage, oedema, hydrocephalus and any malformation. CSF and cranial ultrasound held temporarily in patients with severe cardio-respiratory compromise. Serum urea/ creatinine, liver function tests (LFT's), reticulocyte0 count, Coomb's test, blood culture and urine for reducing substances were done in selected cases guided by history, examination and initial investigations to reach the final diagnosis. TORCH screening was done in neonates with low birth weight, microcephaly, cataract, chorioretinitis, hepatosplenomegally and jaundice. CT scan was done in patients with bulging anterior fontanel and focal neurological deficit and seizure resistant to antiepileptic drugs. Serum magnesium level was done in patients with hypocalcaemia not responding to parenteral calcium administration.

Benign 5th day fit was considered in healthy neurological normal newborns with normal investigations that occurred between 2–5 days of birth and settled without any medication. The data was collected on a Performa.

The data was analysed using SPSS-10. Descriptive statistics and frequencies were used for appropriate parameters.

RESULTS

Neonatal seizures were more common in males (68%) than females (32%) (Table-1). The neonates' ages ranged from 4 to 7 (5.30±6.59) days. Term infants were affected more (90%) compared to preterm infants (10%). The neonates' weight ranged from 2.44 to 2.68 (2.56±0.57) Kg. Out of 100 patients 35% were low birth weight, while 66% of low birth weight were male and 33% were female. All neonates with weight >3.5 Kg were male. The mean length of the neonates was 48.24±3.04.

Most (81%) of the neonatal seizures occurred in the first week of life. Majority (69%) of the 1st week seizures were seen during initial 72 hours. First day seizures were seen in 36%, the second or third day in 20%, and 3–7 days in 25%. Most (23%) of the Neonatal Seizures were found in the month of May followed by June and April. The least frequent seizures were noted in December and August. Frequency of types of seizures was generalised tonic clonic 28%, multi focal clonic 25%, subtle 21%, focal clonic 20%, and myoclonic and focal tonic 3% each. Generalised tonic fits were common (75%) in males while focal tonic fits in females (67%). No significant gender difference was seen in clonic or tonic seizures (p>0.05). Subtle and Myoclonic seizures occurred more (67%) in males (Table-1). Generalised tonic clonic and focal clonic fits (30% each) were the two major types in premature, while generalised tonic clonic (28%) and multi focal clonic (26%) in full term infants (Table-2).

Frequency of causes of fits was birth asphyxia (46%), sepsis (29%), metabolic disorder (23%), kernicterus (6%), hydrocephalus and tetanus (5% each), intracranial bleed (3%) and brain malformations (5%) (Table-3). Focal clonic (28%) and multi-focal clonic seizures (26%) were the most common type of seizures associated with perinatal asphyxia. Subtle (21.7%) and generalised tonic fit (19.5%) were the next common type in HIE (Table-4). Most (72%) deliveries were conducted at hospital and the rest at home. Deliveries conducted by doctor constituted 70%, Dai 26% and LHV 4%. Normal vaginal deliveries were conducted in 67%, Caesarean Section in 17% and assisted deliveries in 16%. Most (51%) were breastfed while 3% formula, cow, and goat milk fed each and rest of neonates no feed was given. As much as 81% neonates had feeding difficulty, 42% had fever, 48% were cyanosed, 21% jaundiced and 7% were dysmorphic.

Table-1: Gender distribution of seizure type (p>0.05)

Seizure Type		Total	Gender			
			Male	%	Female	%
Clonic	Focal	20	14	70	6	30
	Multifocal	25	16	64	9	36
Tonic	Focal	3	1	33	2	67
	Generalised	28	21	75	7	25
Subtle		21	14	67	7	33
Myoclonic		3	2	67	1	33
Total		100	68	68%	32	32%

Table-2: Seizures according to gestational age

Seizure Type		Total	Gestational Age			
			Pre-term	%	Full-term	%
Clonic	Focal	20	3	15	17	85
	Multi-focal	25	2	8	23	92
Tonic	Focal	3	0	0	3	100
	Generalised	28	3	11	25	89
Subtle		21	2	10	19	90
Myoclonic		3	0	0	3	100
Total		100	10		90	

Table-3: Aetiological distribution of clinical neonatal seizures (n=100)

Aetiology	No.	%
Birth Asphyxia	46	46
Septicaemia/ Meningitis	29	29
Metabolic Abnormalities	23	23
Intracranial haemorrhage	4	4
Kernicterus	6	6
Tetanus	5	5
Hydrocephalus	5	5
Brain Malformation	3	3
Fifth day fit	1	1
Encephalitis	1	1
Birth trauma	1	1
Turner Syndrome	1	1

Table-4: Type of fits in birth asphyxia (n=46)

Type		No. (%)
Clonic	Focal	13 (28)
	Multi-focal	12 (26)
Tonic	Focal	1 (6.5)
	Generalised	9 (19.5)
Subtle		10 (21.7)
Myoclonic		1 (2.1)

Table-5: Documentation of clinical parameters in study group (n=100)

Parameter	Documented (%)	95% CI
Fits	100 (100)	
Fever	42 (42)	(33.2–.8%)
Rash	10 (10)	(4.1–15.9%)
Feeding Difficulty	81 (81)	(73.3–88.7%)
Temperature >100 ºF	42 (42)	(33.2–50.8%)
Jaundice	21 (21)	(13–29%)
Cyanosis	48 (48)	(38.2–57.8%)
Dismorphic Features	7 (7)	(2–12%)
Coma	23 (23)	(14.75–31.25%)
Drowsy	59 (59)	(49.36–68.64%)
Hepatomegaly	7 (7)	(2–12%)
Splenomegaly	4 (4)	(0.16–7.84%)
Tachypnoea	7 (7)	(2–12%)
Apnoea	15 (15)	(8–22%)

Table-6: Comparison of aetiology with other studies

Aetiology	Present study	Malik *et al*	Park *et al*	Jin *et al*
Birth Asphyxia	46%	35%	32.9%	65%
Septicaemia/ Meningitis	29%	34%	9.6%	-
Metabolic abnormalities	23%	12.5%	32.9%	5%
Intracranial haemorrhage	4%	9.5%	5.5%	10%
Kernicterus	6%	4.5%	-	-
Tetanus	5%	-	-	-
Hydrocephalus	5%	1.5%	-	-
Brain Malformation	3%	1%	-	6%
Fifth day fit	1%	1%	6.8%	3%
Encephilitis	1%	-	-	-
Birth trauma	1%	-	-	-
Turner Syndrome	1%	-	-	-

Table-7: Comparison of preterm and full-term neonatal seizures [n(%)]

Seizure Type	Gestational Age			
	Present study		Holanda *et al*	
	Premature	Full term	Premature	Full term
Clonic	5 (50)	40 (44)	15 (50)	12 (16.2)
Tonic	3 (30)	28 (31)	10 (33.3)	20 (27)
Subtle	2 (20)	19 (21)	8 (26.6)	54 (72.9)
Myoclonic	0	3 (4)	3 (10.0)	4 (5.4)

DISCUSSION

Seizures are the most common neurological disorders in the neonates.[2] The incidence of neonatal seizures as reported by various studies range from 0.1–0.5% in term neonates 10 and 10–22.7% in preterm neonates.[14]

Malik *et al*[5], Park *et al*[15] and Alcover *et al*[16] described neonatal seizures as more prevalent in males. This is consistent with our study. Seizures were reported to be more common in the first 10 days of life.[5,17] Our findings are consistent with this too. Occurrence of fits in first week and in first 72 hours of life was noted by us as well as earlier researchers.[18] Neonatal seizures are more common in preterm babies[1,15,19] but we found seizures commonly in term babies (90%) as seen in another local study[5]. This may be due to increased survival of premature babies in developed countries.

Most common seizures type is subtle followed by multi-focal clonic[8,20,21] but we found multi-focal clonic and generalised tonic clonic as the common seizure type. This is consistent with the study of Arpino *et al* and Ajay K *et al*[17,18] Ronan *et al* reported that tonic seizures predominated in full term and clonic seizures were equally common in both groups, i.e., full term and preterm[22]. In preterm, the present study show the generalised tonic clonic and focal clonic (30% each) were the most common seizure type followed by subtle and multi-focal clonic seizures (20%) each as also reported by Ajay K *et al*[18] However, Sattar *et al*[23] have reported subtle seizures as the most common type of neonatal seizures in their studies. When the two groups were compared, subtle seizures were most frequently observed in full term. This is in accordance with the literature.[19,21] Subtle and focal clonic seizures were less common types possibly because of poor recognition of subtle and focal clonic seizures by parents or attending health personnel.

Birth asphyxia is the commonest cause of neonatal seizures.[2,9,11] Our findings are in accordance with this. Most seizures in the asphyxiated newborn occur in first 72 hours of life[5,6,16] as in our study. HIE was the predominant aetiology in the full term, causing early-onset neonatal seizures in the first 48 hours of life.[21] When HIE was the likely aetiology, neonaltal seizures had early onset in both term and preterm groups. This finding agreed with reports stressing neonatal asphyxia as the most frequent cause of early onset NS.[20] Whereas Calciolari *et al*[17] reported neonatal asphyxia as the predominant aetiology in both premature and full term neonates. The NS are caused by hypoxic-ischemic encephalopathy in 50–60% of neonates, independent of gestational age, according to Volpe.[20] Out of 46 seizure episodes in babies with perinatal asphyxia 5 were associated with hypocalcaemia, 3 with intracranial bleed and 2 with hypoglycaemia as noted by Butt *et al*.[24] One case each of encephalitis, meningitis, meningocele and kernecterius was responsible for seizure in cases of birth asphyxia while rest of episodes due to HIE alone. The exact contribution of hypoglycaemia and hypocalcaemia as a cause of seizure in babies with perinatal asphyxia is not certain, while in study of Ajay *et al*[18] out of 108 seizure episodes in babies with perinatal asphyxia, 11 episodes and 18 episodes were due to hypoglycaemia and hypocalcaemia respectively.

Perinatal asphyxia caused focal clonic (28%) and multi-focal clonic seizures (26%) in the present study and Ajay K *et al*.[18] as opposed to myoclonic seizures present in 64.7% of cases reported by Mizrahi and Kellaway *et al*[25]. Subtle (21.7%) and generalised

tonic fit (19.5%) were the next common type in HIE. Most of the deliveries were conducted at hospital by doctor and were normal vaginal deliveries as observed in the earlier studies.[26]

Neonatal infections are the important cause of neaonatal seizures.[2] Septicaemia is the second most common cause present in 29% cases.[27] Late onset sepsis was present in 44.8% and early onset sepsis in 55.2% of cases closer to other local study.[5,27] Out of these, four cases were preterm. Meningitis was associated with 59% cases of sepsis while in 41% only sepsis was present. Incidence of pyogenic meningitis is greater with late onset sepsis.[28] We found meningitis in 64.7% cases of late onset sepsis as opposed to 35.3% cases of early onset sepsis as seen by Malik *et al*.[5] PROM was present in 35% of cases with sepsis. Both generalised tonic fit and multi-focal clonic seizures 31% were the most common type of seizures associated with septicaemia as multi-focal clonic noted by Ajay *et al*.[18] Multi-focal clonic followed by focal clonic were the most common types of EONS as observed by Gebremariam A *et al*.[29] Subtle 20% and focal clonic 10% were the next common type in sepsis.

Metabolic abnormalities causing neonatal seizures include hypoglycaemia, hypocalcaemia, inborn error of metabloism[6,28] and pyridoxine deficiency[30]. Metabolic abnormalities contributed to 23% cases of neonatal seizures.[5]

Hypocalcaemia was the commonest cause of metabolic disorder.[5] Early onset hypocalcaemia occurs in first 2–3 days of life.[31] Out of 13 cases, 77% were of early onset type and presented with in first 72-hours of life. Out of these late onset hypocalcaemia babies, 1 was cow-fed and two were breastfed, whereas 6 out of 7 late onset hypocalcaemia seizures were cow-fed in a study by Malik *et al*.[5] Both generalised tonic fit and multi-focal clonic seizures 31% (n=4) were the most common type of seizures associated with hypocalcaemia, while multi-focal clonic were the commonest cause as observed by Ajay *et al*.[18] Focal clonic15% (n=2) and subtle, focal tonic and myoclonic each 8% (n=1) were the next common type in hypocalcaemia.

Incidence of hypoglycaemia as reported in literature varies from 2–26.6%.[16,18,31] In our study it was seen in 8% babies. Seizures due to hypoglycaemia occurred in first 72 hours. Hypoglycaemia was due to IDM in one case, LBW, and prematurely each contributing 2 cases and one case was of Beckwith-Wiedemann syndrome similar to other study.[5] Generalised tonic clonic 75% seizures were the most common type of seizure associated with hypoglycaemia in our study but multi-focal clonic seizures were the most common seizure type observed by Ajay *et al*.[18]

Tetanus was present in 6% of patients. All of these were home delivery. Unvaccinated and handling by Dai are the risk factors as observed by Ijaz *et al*.[32] It is one of the highest figure documented due to lack of immunization of the mothers, unhygienic deliveries by untrained 'Dais'/birth attendants and cutting the umbilical cord with unhygienic and un-sterilised objects, lack of care of umbilical stump and application of materials over the umbilical stump. Risk factors for poor outcome after developing neonatal tetanus were un-immunized mothers' rapid onset and shorter incubation period. Its incidence can be reduced by eliminating the risk factors.

Kernicterus was present in 6% cases in our study whereas 4.5% were reported by Malik *et al*.[5] Its incidence can be reduced by early detection, referral and prompt management of jaundiced newborn. Rh and ABO incompatibility was present in 33.3% cases each while crigeller najar and septicaemia in 1 case as noted by Malik *et al*.[5]

Birth trauma, contributor to intracranial bleed is an important cause of neonatal seizures[33] and is associated with intrumental deliveries by LHV, so good antenatal care and deliveries by an experienced person can reduce the incidence of birth trauma and hence intracranial bleed and neonatal seizures. Intracranial bleed was present in 4% cases as observed by others.[5,18] Common cases were birth trauma in 25% haemorrhagic disease of newborn 25% and septicaemia with DIC 25% (n=1) and IUGR in 25% cases.

CT scan was found superior to cranial ultrasound for the detection of intracranial bleed. Intraventricular haemorrhage was the most common type of intracranial bleed related to the anatomy of germinal matrix, distribution and regulation of cerebral blood flow and structure and vulnerability of periventricular capillaries. Other common sites are intra-cortical and the subdural space.[28,33]

Brain malformations are a rare case of neonatal seizures[28,34] present in 1.5% (n=3) cases. The reported incidence of undetermined aetiology of clinical seizures varies from 2.4–5.3%.[21] Out of 100 cases only 1% (n=1) cases were of presumed idiopathic benign 5th day fit while definite cause was present in remaining 99% (n=99) cases suggesting that in contrast to older children neonatal seizures are rarely idiopathic.[9] In the studies where higher percentage of babies with no definite cause of clinical seizures could be ascertained is due to non-availability of in-house USG cranium, investigations and EEG facilities, short period survival between first seizure episode and death etc.

The results were compared with the study of Jin *et al*[28], Malik *et al*[5] and Park *et al*[35] (Table-7). HIE was the commonest cause in all the studies compared, while septicaemia was common in our study due to the increased risk of neonatal infections in our set up, that can be reduced by improving sterilisation techniques in the NICU. Compared with our study, brain malformations were more commonly identified in the

study of JIN *et al*[28] probably due to the non-availability of advanced neuro-imaging facilities including MRI in our setup. Neonatal seizures associated with transient metabolic abnormalities, 5th day fit and the subarachniod bleed have the best prognosis while those with the birth asphyxia and the brain abnormalities and the inborn errors of metabolism have the worst prognosis.[9] Patients with meningitis have intermediate prognosis.[36]

CONCLUSION

Tonic clonic seizure was the commonest type of neonatal seizure. Birth asphyxia, septicaemia with or without CNS infection, transient metabolic disorder, and intracranial bleed were found to be common causes.

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Address for Correspondence:

Dr. Shahzad Najeeb, Department of Paediatrics, Ayub Teaching Hospital Abbottabad, Pakistan. **Cell:** +92-334-8981399
Email: drshazad628@yahoo.co.in