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Original Research Article

Etiological Profile of Neonatal Seizures and Prognostic Factors for Adverse Outcome: A Single Center Prospective Study

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ABSTRACT:

Introduction: Neonatal seizure is the most common manifestation and an important determinant of outcome of neurological disorders in newborn period. This study aims to delineate the etiological profile and neurodevelopmental outcome of neonatal seizures and also to identify predictors for adverse outcome.

Methods: One hundred and seventeen neonates with clinically proven seizures admitted in Dhulikhel Hospital from February 2014 to February 2016 were recruited. All of them underwent necessary neurological diagnostic tests. The survivors were followed up for at least three times within the first 18 months of life. Prognostic value of factors for adverse outcomes were analyzed with Chi square test and binary logistic regression analysis.

Results: Among a total of 954 neonates admitted, 117 (12.26%) developed clinical seizures. The most common cause of neonatal seizure was hypoxic ischemic encephalopathy (n=69, 59%), followed by infection (n=20, 17.09%), and metabolic disturbances (n=16, 13.7%). The outcomes were mortality (n=16, 13.7%), post neonatal seizure (n=18, 15.4%), developmental delay (n=31, 26.5%), vision impairment (n=19, 16.2%) and hearing impairment (n=26, 22.2%). Low Apgar scores at one minute (p=0.03) and five minutes (p=0.001), early onset seizure (p<0.001), and more than one drug used for seizure control (p=0.001) were early prognostic factors for adverse outcome.

Conclusion: Birth asphyxia followed by infection and transient metabolic disturbance were common etiologies for neonatal seizures. Low Apgar scores at one and five minutes, early onset seizure, multiple episodes of seizures and requirement of multiple anti-epileptics to control seizures were found to be significant predictors for adverse neurodevelopmental outcome.

Keywords: APGAR score, developmental delay, hypoxic ischemic encephalopathy, neonatal seizure

INTRODUCTION:

Neonatal seizures are usually an acute manifestation of disturbance of the developing brain and common in the early weeks of life. The incidence of seizure varies widely in different countries ranging from 1.8 to 5 per 1000 live births in the United States of America to 39.5 per 1000 live births in Kenya.[1,2] The predominant causes of neonatal seizures are hypoxic ischemic encephalopathy (HIE), followed by metabolic abnormalities, infection, intracranial hemorrhage and developmental abnormalities.[3,4]

Several prognostic factors for adverse outcome of seizure are well known, namely brain immaturity, abnormal cranial ultrasonography (USG) findings, low Apgar score, early onset of seizure or prolonged duration of seizure.[5] Neonates with seizures are at an increased risk of mortality, and the survivors are at risk of neurological sequelae as developmental delay, epilepsy and cognitive impairment. We therefore need to initiate an early diagnostic work up to establish etiology, depending on the available facilities.[6] Establishing risk factors that might predict outcome of newborn with seizure would be helpful in planning long term follow up and health assistance to these children.

Many studies have been published on risk factors, etiology and outcome of newborns with seizure from different countries. However, there is

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a paucity of literature from our country that have examined the causes, risk factors and outcomes of neonatal seizures. The aims of the current study are to describe the etiologic profile, neurodevelopmental outcome and reliable prognostic indicators of outcome of infants surviving neonatal seizures.

METHODS:

This was an observational prospective study in a cohort of newborns with clinically proven seizures. The survivors were followed up in our high risk outpatient clinic for at least 18 months. Newborns included in the study were neonates with seizures admitted in the Neonatal Intensive Care Units (NICU) of Dhulikhel Hospital from February 2014 to February 2016. Ethical approval for the study was obtained from Institutional Review Committee of Kathmandu University School of Medical Sciences.

Seizures were defined as reported or observed repeated involuntary muscle contractions, abnormal tonic extensions or jerky movements of any part of the limb, face or mouth that was not stimulus sensitive or repetitive abnormal chewing, ocular or pedalling movements. Seizures were then classified after clinical observation and correct description of seizure type.

The time of occurrence of the seizure was categorized according to the age at onset as seizure occurring within the first 24 hours, between 24 to 72 hours and after 72 hours. It was considered early if seizures started within 72 hours of life and late if started after 72 hours. The frequency of seizure was also recorded as single or multiple episodes. Gestational age was determined according to modified Ballard scale.[7] The different modes of delivery were also recorded. The Apgar scores at one and five minutes after birth were noted. Maternal risk factors as family history of neonatal seizure, maternal illness, maternal medication, complications during pregnancy (prolonged second stage of labour and placental or cord complications) were also recorded.

The primary etiology of the seizure was ascertained through clinical history, neuroimaging studies [computer tomography (CT), cranial USG and/or magnetic resonance imaging (MRI)] when indicated. Laboratory tests as cerebrospinal fluid (CSF) analysis , serum glucose, serum electrolyte level and arterial blood gas analysis were done in required cases. Some infants underwent Toxoplasma gondii, Rubella, Cytomegalovirus and Herpes simplex virus (TORCH) screen for congenital infection. Diagnosis of neonatal sepsis was based on clinical manifestations, sepsis work-up and positive blood culture.

Cranial USG was done in almost all infants. Some had at least one additional modality of imaging, such as cranial CT or MRI. The intracranial hemorrhage group included infants with extra-axial (epidural, subdural and subarachnoid) hemorrhage or intra-parenchymal hemorrhage. Developmental cerebral defect, cerebral infarction and hydrocephalus if any present, were also documented.

We divided etiology into seven groups: (1) Hypoxic ischemic encephalopathy (HIE), (2) transient metabolic disturbance, (3) infection, (4) intracranial hemorrhage, (5) developmental cerebral defect, (6) benign familial neonatal seizure and (7) unknown etiology, if diagnostic evaluation revealed no etiology.

The drug of first choice was intravenous phenobarbitone at a loading dose of 20-40 mg/kg and a maintenance dose of 3-8 mg/kg/day. In case of persistence or recurrence of seizures, we administered intravenous phenytoin at a loading dose of 20mg/kg and a maintenance dose of 4-8 mg/kg/day. If seizure still persisted, continuous intravenous infusion of midazolam at 1-10 microgram/kg/day was given. Few neonates had to be ventilated because of refractory seizure despite continuous infusion of midazolam. The number of antiepileptic drugs (AED) needed for control of seizures was also recorded.

All the survivors were followed up for at least three times in the first 18 months of life i.e. around two months, between six and nine completed months and between 11 and 18 completed months in the High-Risk Clinic of Pediatric outpatient department. They were evaluated thoroughly by physical examination and developmental assessment. At the same time infants were seen by physiotherapist, ophthalmologist and audiologist whenever necessary. In this study we evaluated the outcome by developmental progress, growth of head, visual impairment, hearing impairment and the presence of seizure after NICU discharge.

Statistical analysis:

Data were entered to and analyzed using Statistical Package for Social Sciences (SPSS™)

Table 1. Outcome of neonatal seizures in different clinical conditions (N=117)

Variables		Normal outcome	Adverse outcome	Statistics
Sex	Male	44	35	X^2 (df=1, N=117)= 0.245, p=0.621
	Female	23	15	
Gestational age	Term	59	41	X^2 (df=1, N=117)=0.847, p=0.358
	Preterm	8	9	
Mode of delivery	Vaginal	43	30	X^2 (df=2, N=117)=2.508, p=0.285
	Cesarean section	22	15	
	Instrumental	2	5	
Onset of seizures	Within 24 hours	20	32	X^2 (df=2, N=117)= 15.207, p= <0.001
	24 to 72 hours	25	6	
	After 72 hours	22	12	
Apgar at 1 min	0-3	17	27	X^2 (df=2, N=117)=11.665, p=0.003
	4-6	31	18	
	7-10	19	5	
Apgar at 5 mins	0-3	1	7	F (df=2, N=117)=14.096, p=0.001
	4-6	27	29	
	7-10	39	14	
Type of seizure	Subtle	16	16	X^2 (df=3, N=117)=20.696, p=<0.001
	Tonic	35	12	
	Clonic	13	6	
	Mixed	3	16	
Episodes of seizure	Single	56	6	X^2 (df=1, N=117)=58.896, p=<0.001
	Multiple	11	44	
AED	Single	63	16	X^2 (df=1, N=117)=50.237, p=<0.001
	Multiple	4	34	
Neuroimaging	Normal	18	10	X^2 (df=1, N=44)=2.946, p=0.086
	Abnormal	6	10	

version 16. Quantitative data were presented in mean ± SD and qualitative data in frequency and percentages. The association of neonatal seizures in different clinical conditions were assessed by Pearson Chi square test and Fisher's exact test. The risk factors for different adverse outcomes were assessed applying binary logistic regression analysis. P value less than 0.05 was considered significant.

RESULTS:

Among total neonates admitted to NICU during the study period, 117 (12.26%) neonates had developed clinical seizure. Seventy five (64.1%) neonates were male and 42 (35.9%) were female. The male to female ratio was 1.7:1. One hundred (85.47%) neonates were term, whereas 17(14.52%) were preterm. The mode of delivery in 73 (62.39%) neonates was vaginal delivery , 37 (31.62%) was cesarean section (CS) and 7 (5.98%) was instrumental delivery. Twenty seven (23.07%) neonates were born to mother who had history of prolonged second stage of labor and nine (7.69%) to those with history of placental or cord complications. Fifty two (44.44%) neonates had first episode of seizure before 24 hours, 31 (26.49%) between 24 and 72 hours and 34 (29.05%) after 72 hours (late onset). In this study, 62 (53%) neonates had single episode of seizure while 55 (47%) had multiple episodes of seizure. Abnormal neuroimaging were seen only in 11 (9.4%) neonates. Among all neonates 78 (66.66%) needed only one antiepileptic medication to control seizure while 39 (33.33%) needed multiple drugs (Table 1).

The most common etiology for neonatal seizure was birth asphyxia (n=69, 59%), followed by infection (n=20, 17%) and transient metabolic disturbance (n=16, 13.7%). There was one neonate with no identified etiology (Fig.1).

Sixteen (13.67%) patients died during or after neonatal period. Among 101 neonates discharged after survival, 18(15.4%) patients had repeated seizures during the follow up period, 31(26.5%) had developmental delay, 19(16.2%) had vision impairment and 26(22.2%) had hearing impairment. Low Apgar score at one minute (p=0.003), Low Apgar score at five minutes (p=0.001), early onset of seizures (p<0.001), multiple episodes of seizure (p<0.001), multiple anti-epileptics used to control seizure (p<0.001) were notable risk factors for adverse outcome (Table 1).

Analysis of various risk factors for developmental delay by binary logistic regression showed that neonates with single episode of seizure were less likely to develop developmental delay

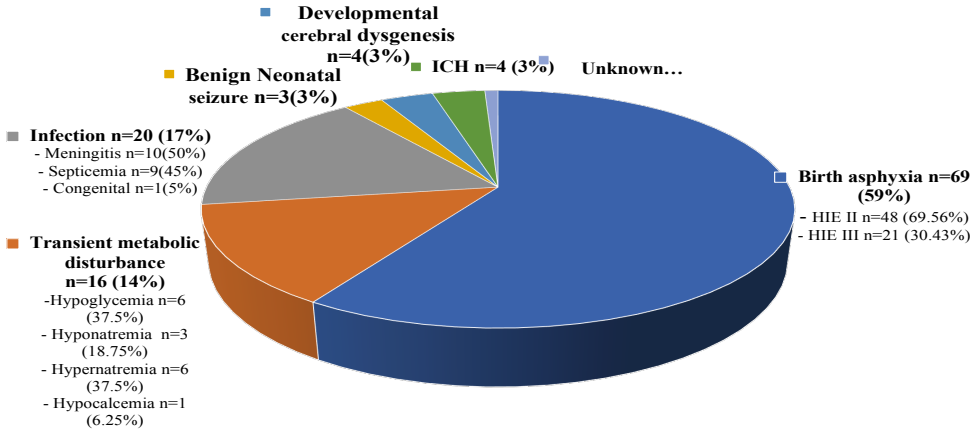

Fig. 1. Etiological Distribution of Neonatal Seizure (N=117)

as compared to multiple episodes of seizure [AOR (95%CI)=0.00(0.00-0.67), p=0.044]. The odds of having developmental delay was 33% to 100% lower in those neonates with single episode of seizure in comparison to multiple episodes. The incidence of developmental delay was high among the neonates whose Apgar score was low at one minute and among those that developed seizure within 24 hours; however, these findings were statistically not significant (Table 2).

Post neonatal seizures were more common in male term babies delivered vaginally; however, it

Table 2. Risk factors for developmental delay (N=117)

Variables		Frequency (%)	AOR (95% CI)	p value
Sex	Male	67(66.33)	45938(0.087-2.4E+10)	0.110
	Female	34(33.66)		
Gestational age	Term	88(87.12)	0.00(0.00-2.20)	0.073
	Preterm	13(12.87)		
Mode of delivery	Vaginal delivery	64(63.36)	101.14(0.00-9.47E+7)	0.424
	C.S	32(31.68)	19.01(0.00-1.71E+7)	0.510
	Instrumental delivery	5(4.95)		0.674
Apgar Score at 1 min	0-3	32(31.68)	0.20(0.00-461.91)	0.809
	4-6	47(56.53)	0.13(0.00-70.29)	0.685
	7-10	22(21.78)		0.528
Apgar score at 5 mins	0-3	4(3.96)	4.8E+11(0.00-1.2E+29)	0.182
	4-6	47(46.53)	1650291(0.40-6.6)	0.188
	7-10	50(49.50)		0.065
Maternal risk factors	Prolonged second stage of labour	19(18.81)	0.012(0.00-28.98)	0.267
	Placental or cord complications	8(7.93)	0.11(0.003-4.79)	0.252
Onset of seizure	<24hours	39(38.61)	0.012(0.00-2.36)	0.100
	24-72 hours	30(29.70)	0.00(0.00-1.57)	0.062
	>72 hours	32(31.68)		
Episode of seizure	Single	62(61.38)	0.00(0.00-0.67)	0.044
	Multiple	39(38.68)		
Abnormal neurological finding	Yes	11(29.72)	326(0.33-3270842)	0.218
	No	26(70.27)	1155.79(0.25-5.37E+7)	0.198
Antiepileptic medication	Single	77(76.23)	0.001(0.00-7.94)	0.137
	Multiple	24(23.76)		

Table 3. Risk factors for post neonatal seizure (N=117)

Variables		frequency (%)	AOR (95% CI)	P value
Sex	Male	67(66.33)	0.374 (0.022-6.337)	0.495
	Female	34(33.66)		
Gestational Age	Term	88(87.12)	0.574 (0.028-11.757)	0.718
	Preterm	13(12.87)		
Mode of delivery	Normal vaginal delivery	64(63.36)	0.229 (0.001-38.077)	0.572
	C.S	32(31.68)	0.816 (0.004-164.363)	0.940
	Instrumental delivery	5(4.95)		0.551
Apgar Score at 1 min	0-3	32(31.68)	104 (1.24-870)	0.043
	4-6	47(56.53)	8.28 (0.34-200)	0.193
	7-10	22(21.78)		0.123
Apgar Score at 5 mins	0-3	4(3.96)	205162 (0.00-1.17)	0.997
	4-6	47(46.53)	0.28 (0.007-12.09)	0.514
	7-10	50(49.50)		0.808
Maternal risk factors	Prolonged second stage of labour	19(18.81)	1.8 (0.10-31.40)	0.669
	Placental or cord complications	8(7.93)	2.48E+9 (0.00)	0.998
Onset of seizure	<24hours	39(38.61)	0.11(0.03-3.74)	0.220
	24-72 hours	30(29.70)	1.09 (0.08-14.65)	0.948
	>72 hours	32(31.68)		
Episode of seizure	Single	62(61.38)	0.00 (0.00-)	0.994
	Multiple	39(38.68)		
Abnormal neurological finding	Yes	11(29.72)	0.177(0.08-3.77)	0.268
	No	26(70.27)	0.437 (0.16-11.65)	0.621
Antiepileptic medication	Single	77(76.23)	0.64(0.07-5.67)	0.689
	Multiple	24(23.76)		

was not statistically significant. Low Apgar score (0-3) at one minute was the single most risk factor for post neonatal seizure(p=0.043). The neonates with low Apgar score (0-3) had 104 times more odds of developing post neonatal seizures in comparison to those with normal Apgar score (7-10) (Table 3).

Multivariable binary logistic regression analysis showed that multiple episodes of seizure (p<0.001) and Apgar score (4-6) at five minutes (p=0.046) were statistically significant risk factors for hearing impairment. Similarly, mode of delivery especially vaginal delivery (p=0.01) and cesarean section (p=0.03) were less likely to result in vision impairment in comparison to instrumental delivery. Multiple episodes of seizure (p=0.005) and abnormal neurological findings (p=0.045) were also found to be statistically significant risk factors for vision impairment (Table 4).

DISCUSSION:

The overall incidence of neonatal seizures in our study was 12.26%. This incidence is similar to that in established intensive care units which is as high as 25% in NICU.[8] The seizures were more common in males (63.36%) which is similar to the study done by Alyasiri AA[9](63.9%), Sabzehaei et al.[3] (57%) and Jasim M et al.[4](54.5%).The majority of neonates who developed seizures were full term (85.47%) which is comparable to the finding of Alyasiri AA (91%).[9] A majority of neonates in

Table 4. Risk factors for vision and hearing impairment (N=117)

		Frequency (%)	Hearing impairment AOR (95% CI)	p value	Vision impairment AOR (95% CI)	p value
Sex	Male	67 (66.33)	10.77 (1.41-82.71)	0.022	6.27 (0.79-49.70)	0.08
	Female	34 (33.66)				
Gestational Age	Term	88 (87.12)	0.765 (0.07-7.86)	0.822	0.14 (0.01-1.70)	0.12
	Preterm	13 (12.87)				
Mode of delivery	vaginal delivery	64 (63.36)	0.58 (0.02-12.2)	0.73	0.004 (0.00-0.38)	0.01
	C.S	32(31.68)	0.24 (0.01-5.34)	0.37	0.009 (0.00-0.63)	0.03
	Instrumental delivery	5 (4.95)				
Apgar Score at 1 min	0-3	32 (31.68)	2.70 (0.09-81.61)	0.56	17.40 (0.33-915)	0.15
	4-6	47 (56.53)	3.63 (0.29-45.04)	0.31	2.54 (0.18-35.03)	0.48
	7-10	22 (21.78)				
Apgar Score at 5 mins	0-3	4 (3.96)	25.43 (0.45-1409)	0.114	42.02 (0.69-255)	0.07
	4-6	47 (46.53)	10.66 (1.03-109)	0.046	7.69 (0.45-131.55)	0.15
	7-10	50 (49.50)				
Maternal risk factor	Prolonged second stage labor	19 (18.81)	0.77 (0.12-4.90)	0.78	4.13 (0.30-56.38)	0.28
	Placental or cord complication	8 (7.93)	2.69 (0.15-47.75)	0.49	0.11 (0.005-2.841)	0.18
Onset of seizure	<24hours	39 (38.61)	1.20 (0.12-11.47)	0.86	0.07 (0.003-1.584)	0.09
	24-72 hours	30 (29.70)	1.03 (0.14-7.59.0)	0.97	0.96 (0.108.95)	0.97
	>72 hours	32 (31.68)				
Episode of seizure	Single	62(61.38)	0.014 (0.002-0.124)	<0.001	0.002 (0.00-0.15)	0.005
	Multiple	39(38.68)				
Abnormal neurological finding	Yes	11 (29.72)	0.46 (0.05-3.81)	0.47	0.121 (0.16-0.016)	0.045
	No	26 (70.27)				
Antiepileptic medication	Single	77 (76.23)	1.32 (0.19-8.89)	0.77	1.03 (0.13-7.78)	0.97
	Multiple	24(23.76)				

our study population were born via vaginal delivery (62.39%). Similar results were also seen in the study done by Talebian A et al. in Iran with seizure incidence in vaginal delivery of 65.61% compared to 34.4% in CS.[10] We found that 52(44.44%) of the neonates had seizure of early onset. This is similar to the findings of Faiz N et al.[8] in which early onset seizure was found in 59% and in another study by Alyasiri AA [9] where early onset seizure was found in 50.8%.

In our study, perinatal asphyxia was the leading cause of neonatal seizures (59%) although the incidence varies in different studies as a result of the inconsistent diagnostic criteria used. This finding is comparable to studies by Sahana et al.[11] and Loman AM et al.[12]in which neonatal seizures following HIE had occurred in 57.8% and 53.9% respectively. Infections were the second most common cause of seizure in our study which comprised almost 17.09% which was similar to study by Alyasiri AA (16.4%). [9] Another common cause of neonatal seizure in the current study was transient metabolic disturbance

(n=16, 13.6%), which was comparable to studies by Sahana et al.[11] In our study, hypoglycemia was the most common transient metabolic disturbance (n=6) comprising 5.12% of total etiology and 37.5% of transient metabolic disturbance. This was supported by the other studies as well.[9,10]

In this study, beside three major etiologies, the other etiologies for seizure were intracranial hemorrhage, developmental cerebral dysgenesis and benign neonatal seizure. Many other studies reported similar findings.[9,13]

We found statistically significant relationship between low Apgar scores (0-3) at one and five minutes, early onset seizure (<24 hours), multiple episodes of seizure, number of antiepileptic drugs needed to control seizure and neonatal outcome. Similar to our study, other studies by Lai YH et al.[14] and Pisaniet F et al.[15] found that low Apgar scores at one and five minutes and early onset of seizure were prognostic factors for poor outcome. We did not find a significant relationship between abnormal neuroimaging finding and seizure outcome (p=0.086). This finding differs from other reports in which abnormal neuroimaging has been associated with worse outcome.[14,15] This could possibly be explained by the fact that only minor anomalies were found in neuroimaging in most of the neonates and only few neonates had major malformations or pathological conditions.

The only variable significantly related to developmental delay was multiple episodes of seizure (p=0.044). The finding differs from other reports in which abnormal neuroimaging and prematurity were significantly related to developmental delay while multiple episodes was not.[13] Developmental delay was more dependent on etiology and duration of seizure rather than the episode of seizure. Similar to our study, another study by Echandia et al. showed low five minutes Apgar score was not an effect modifier neither a confounder of the association between neonatal seizure and developmental delay. [16]

The only variable significantly related to post neonatal seizure was low Apgar score at one minute. Eighteen (15.4%) newborns recruited to our study developed seizure later in life which is comparable to the study done by Francesco P et al.[17]where 17.6% of the newborns developed epilepsy later in life. The study also showed no significant relation of mode of delivery, gestational age and onset of seizure with post neonatal seizure similar to our study.

The present study found significant occurrence of hearing loss among infants with the history of low Apgar score at five minutes. This finding was similar to another study done in Gauhati Medical College Hospital, India.[18] Similar to another study by Pisani F et al.[15] this study also showed association of multiple episodes of seizure with poor neurologic outcome including vision and hearing loss.

Limitation:

Since neonatal seizures are often subclinical, EEG recording of electrographic seizures is crucial for estimation of true seizure burden which could not be done in our setup. The number of neonates was less as it was a single center study and follow up was not done for longer periods.

CONCLUSION:

The most common cause of neonatal seizures was HIE followed by infection and transient metabolic disturbances. Neonatal seizures predominated in term, male newborns and vaginal delivery with low Apgar score. Furthermore, the follow up showed an increased risk of developmental delay and hearing impairment in most infants. We found five variables in neonates with neonatal seizures for providing early prognostic information on adverse outcome: low Apgar scores at one and five minutes, early onset seizure, multiple episodes of seizures and multiple anti-epileptics needed to control seizures.

Conflict of interest:

The authors declare that no competing interests exist.

Financial Disclosure:

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