

Etiology, Clinical Features, And Short-Term Outcome Of Seizures In Newborns Admitted To The University Of Gondar Hospital, Ethiopia

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Background: Neonatal seizures are the most common neurological dysfunction in the neonatal period. Neonatal seizure patterns and short-term neurologic outcomes, particularly in the Ethiopian context, have not been adequately studied.

Objective: The main aim of this study is to assess the pattern, probable etiology, short-term outcomes, and determinants of neonatal seizures in the neonatal intensive care unit of Gondar University Specialized Comprehensive Hospital.

Methods: A hospital-based prospective observational cohort study was conducted from October 1, 2016, to September 30, 2018.

Results: Among the 117 neonates enrolled, the most common type of neonatal seizure was subtle (60.6%), followed by tonic (15.4%), and clonic (12.8%) seizures. The most common etiology for the seizure was perinatal asphyxia (PNA) with hypoxic-ischemic encephalopathy (HIE; 74.4%) followed by electrolyte disturbances (12.8%). In the follow-up, 23 (19.7%) died during the acute neonatal illness. The most common cause of death was PNA with HIE, accounting for 73.9% of the deaths. Among the surviving newborns, 10 (10.6%) had neurodevelopmental deficits at discharge. Being a multiparous mother (OR= 0.172; 95% CI: 0.033, 0.880), being female (OR= 0.171; 95% CI: 0.055, 0.538), and having tonic (OR= 0.164; 95% CI: 0.030, 0.885) and myoclonic seizures (OR= 0.040; 95% CI: 0.055, 0.538) were significantly associated with mortality poor short-term outcome.

Conclusion: Subtle seizures were the most common seizure semiology. The most common etiology for seizure was PNA with HIE. Parity, gestational age, neonatal sex, and seizure type were determinants of short-term outcomes.

Keywords: hypoxia-ischemic encephalopathy, neonatal seizures, newborn, etiology, mortality

Introduction

Neonatal seizures are the most common neurological disorder in the neonatal period. Seizures are a paroxysmal alteration in neurological functions like motor, behavior, and/or autonomic function and can occur at any gestational age. Neonatal seizures often indicate an underlying neurologic disturbance. They require an immediate assessment to determine the underlying cause and necessary interventions.¹

Seizures are a potentially life-threatening problem with a variety of causes. Thorough and timely evaluations of seizures are necessary to identify and treat the underlying etiology, thereby reducing potential morbidity and mortality.

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Studies from different low-income countries showed that perinatal asphyxia with hypoxic-ischemic encephalopathy (HIE) is the most common cause.²⁻⁵ Metabolic abnormalities, infection, intracranial hemorrhage, developmental anomalies, and others like inborn errors of metabolism are rare causes of neonatal seizures.^{6,7} They are important to consider as their detection allows appropriate counseling and may permit specific therapy.⁸

Factors associated with neonatal seizures include etiology, type of seizure, status epilepticus, early onset of seizures, gestational age, Apgar score, birth weight, need for resuscitation, neurological examination at the onset of seizure, electroencephalogram (EEG), and radiological findings. The reliability of most of these factors is limited because of different reasons.⁹ However, there are no published studies in Ethiopia regarding neonatal seizure etiology to compare the frequency, probable etiologies, and short-term outcome of neonatal seizures with studies done elsewhere.

The aim of this study is to determine the pattern, probable etiology, and short-term outcome of neonatal seizures in Gondar University Comprehensive specialized hospital neonatal intensive care unit (NICU).

Methods And Subjects

Study Setting And Period

This was a hospital-based, prospective observational cohort study involving the clinical and laboratory data collection conducted in the neonatal intensive care unit of Gondar University hospital from October 1, 2016, to September 30, 2018.

This study was conducted at the University of Gondar Hospital (UoGH), which is one of the largest referral hospitals with access to about 5 million people and also one of the oldest academic institutions in Ethiopia. UoGH is located at the heart of Gondar city in the northwestern part of the country. The NICU was established 20 years ago and serves as a tertiary and a referral unit for the region. It receives high-risk babies delivered within the institution, referrals from other health facilities, and referrals from home deliveries. The number of admitted neonates varies from time to time, with an average of 1500 admissions every year.

Data Collection And Processing

Inclusion Criteria

Any neonates with reported or observed seizure and unequivocal description of seizure by the parents or clinicians were included in the study.

Exclusion Criteria

Neonates with uncertain clinical manifestations like jitteriness, tetanic spasms, and newborns with complex malformations and syndromic presentations were excluded.

After enrolment, baseline characteristics of convulsive neonate, including gender, gestational age, and weight were recorded at admission. A detailed antenatal history, which included history of maternal illness during pregnancy, prenatal history, labor records for evidence of fetal distress, Apgar score, and type of delivery were recorded in a pretested case recording format. Discharge, duration of stay, condition at discharge, and seizure control were recorded.

Operational Definitions

The diagnosis of neonatal seizures is based on clinical observation and an accurate description of the type of seizures. We classified seizures according to the International League Against Epilepsy: subtle, tonic, clonic, myoclonic, and mixed.¹⁰ A complete clinical examination of neonates, blood glucose, total serum calcium, and magnesium levels were done immediately after neonate had seizures and before starting any specific treatment. The seizure etiology diagnosis was based on clinical data, laboratory findings, and/or brain imaging studies. Various criteria for diagnosing metabolic abnormalities were defined as hypoglycemia; blood sugar <40 mg/dL (2.2 mmol/L), hypocalcemia; total serum calcium <7.0 mg/dL (1.7 mmol/L), hypomagnesemia; serum magnesium <1.5 mg/dL, hyponatremia; serum sodium <125 mEq/L, and hypernatremia when it is >150 mEq/L.

The diagnosis of HIE was based on history, physical examination, Apgar score, arterial blood gas, and neuroimaging. The diagnosis of neonatal infection was based on the clinical manifestation, sepsis workup, and positive blood, urine, and/or urine culture. Bacterial meningitis was confirmed by positive CSF cell count or culture. Acute bilirubin encephalopathy was diagnosed by high total serum bilirubin plus clinical manifestations. At the time of discharge, duration of stay, condition at discharge, and seizure control will be recorded. Short-term outcome in this study was defined as an outcome at the time of discharge which is death and neurologic status.

Data Entry, Analyses, And Processing

The extracted data were analyzed using SPSS software package version 21. Frequencies, cross-tabulation, and Chi-square test were used for data analysis. Binary logistic

regression was fitted to identify factors associated with treatment outcome. Variables with p -value <0.25 were fitted to multivariate logistic regression analysis. Odds ratio with the corresponding 95% confidence interval was calculated to show the strength of association. In multivariate analysis, variables with p -value <0.05 were considered statistically significant. Descriptive statistics like percentage, mean, and standard deviation were presented.

Ethical Approval

Ethical clearance was obtained from the Ethical review board of University of Gondar, School of Medicine. All data were collected after the management of the neonate is complete. A written consent was obtained from the mother/father before collecting data and that the study was conducted in accordance with the Declaration of Helsinki.

Results

Socio-Demographic Characteristics Of Patients

A total of 117 patients were included in the study. The demographic data revealed that the number of male and female patients was 86 (73.5%) and 31 (26.5%), respectively. The mean (\pm SD) of age at admission was 55.79 ± 133.36 hrs (2.3 ± 5.6 days). The minimum and maximum age of patients involved was 0.25 hrs and 648 hrs (27 days), respectively (Table 1). The majority of study participants are delivered to mothers in the age range of 25–35 years (53.8%) (Table 2).

Classification Of Neonatal Seizures

Of the 117 study participants, subtle seizures were the most common seizure type (60.6%) followed by tonic seizure (15.4%) and clonic (12.8%) seizure (Table 3).

Possible Etiology Of Seizure

The most common etiology for seizure was PNA with HIE (74.4%) followed by transient metabolic disturbances (hypocalcemia, hyponatremia, hypernatremia) (12.8%) (Table 4). Of all the newborns with seizures, 72.6% of them had a seizure during the first 24 hrs of life (Table 5).

Management Of Neonatal Seizure

Among 27 (23.1%) patients, seizures were controlled with monotherapy (either calcium gluconate or phenobarbital). Dual (calcium gluconate and phenobarbital) and triple

Table 1 Sociodemographic Characteristics Of Study Participants At The University Of Gondar Hospital, NICU, In Northwest Ethiopia, 2016–2018 (n=117)

Variable	Frequency (N)	Percentage
Age at admission in hours		
0–24	82	70.1
25–168	24	20.5
169–672	11	9.4
Sex		
Male	86	73.5
Female	31	26.5
Gestational age		
Preterm	3	2.6
Term	97	82.9
Post term	17	14.5
Weight at admission		
<2500 gm	11	9.4
2500–4000 gm	105	89.7
>4000 gm	1	0.9

(calcium gluconate, phenobarbital, and phenytoin) therapies were used in 50 (42.7%) and 40 (34.2%) patients, respectively. About six (5.1%) need intermittent diazepam to control seizures. Four out of six neonates had subtle seizures.

Duration Of Stay In The Ward

The length of stay in the ward with mean \pm SD was 209.64 ± 134.01 hrs (8.7 ± 5.6 days) with a minimum and maximum of 0.5 days and 25 days, respectively

Outcome

In the follow-up, 23 (19.7%) died during the acute neonatal illness and 10.6% of surviving newborns had neurologic sequelae like motor deficits, spasticity and decreased the level of consciousness at the time of discharge (Table 6). The most common cause of death was PNA with HIE accounting for 73.9% of the deaths. Death is common among babies with the onset of seizure between 24 and 72 hrs of age.

Determinants Of Short-Term Outcome

Multivariate logistic regression output indicated that parity, gestational age, sex of newborn, and type of seizure were significantly associated with mortality as shown in Table 7.

Table 2 Socio-Demographic And Other Characteristics Of Mothers Of Babies With Neonatal Seizures In University Of Gondar Hospital, NICU, In Northwest Ethiopia, 2016–2018 (n=117)

Variable	Frequency	Percent
Age in years		
<25	48	41
25–35	63	53.8
>35	6	5.2
Parity		
Primipara	66	56.4
Multipara	42	35.9
Grand multipara	9	7.7
Address		
Urban	36	30.8
Rural	81	69.2
Educational status		
No formal education	43	36.8
Primary	26	22.2
Secondary	24	20.5
College/university	24	20.5
ANC follow-up		
Yes	110	94
No	7	6
Labor		
Spontaneous onset	105	89.7
Induced	9	7.7
Elective C/S	3	2.6
Duration of labor in hours		
≤3	12	10.3
4–24	83	70.9
>24	22	18.8
Duration of ROM in hours		
<18	99	84.6
≥18	18	15.4
Place of delivery		
UoGH	71	60.7
Primary Hospital	16	13.7
Health center	27	23
Home/on the way	3	2.6
Mode of delivery		
SVD	76	65
Assisted breech	4	3.4
C/S	27	23.1
Instrumental	10	8.5

Abbreviations: SVD, spontaneous vertex delivery; C/s, cesarean section; UoGH, University of Gondar Hospital; ROM, rupture of membrane.

The likelihood of death from neonates having seizures was decreased by 82.8% in multiparous mothers (AOR= 0.172; 95% CI: 0.033, 0.880) as compared with primiparous mothers.

Table 3 Types Of Clinical Seizure In Babies With Neonatal Seizure In Gondar University Comprehensive Specialized Hospital, NICU, 2016–2018 (n=117)

Type of Seizure	Total Cases N	Gestational Age N (%)		
		Term	Preterm	Post Term
Subtle	71 (60.6)	62 (87.3)	2 (3.2)	8 (11.5)
Tonic	18 (15.4)	17 (94.4)	0 (0)	1 (5.6)
Clonic	15 (12.8)	10 (66.7)	1 (6.6)	4 (26.7)
Myoclonic	2 (1.7)	2 (100)	0 (0)	0 (0)
Mixed	11 (9.4)	7 (63.6)	0 (0)	4 (36.4)

The likelihood of survival in neonates with seizure was 42 times higher in terms than preterm (OR= 42.334; 95th CI: 1.326, 1351.3). The odds of death in male neonates with seizure were 5.84 lower than female neonates with seizure (OR= 0.171; 95% CI: 0.055, 0.538).

Table 4 Etiologic Profile In Neonates With Seizure In Gondar University Comprehensive Specialized Hospital, NICU, 2016–2018 (n=117)

Diagnosis	Total Cases (%)	Type Of Seizure, n of cases	Seizure Onset, n of cases
Sepsis	3	Subtle 0 Clonic 2 Tonic 1 Myoclonic Mixed	<12 hrs 12–24 hrs 24–72 hrs 1 72 hrs–7 days 1 7 days–30 days 1
HIE	87	Subtle 54 Clonic 9 Tonic 10 Myoclonic 2 Mixed 11	<12 hrs 36 12–24 hrs 33 24–72 hrs 15 72 hrs–7 days 1 7 days–30 days
Meningitis	10	Subtle 2 Clonic 4 Tonic 4 Myoclonic 0 Mixed 0	<12 hrs 12–24 hrs 24–72 hrs 72–7 days 2 7 days–30 days 8
Metabolic	15	Subtle 14 Clonic 0 Tonic 1 Myoclonic 0 Mixed 11	<12 hrs 15 12–24 hrs 24–72 hrs 72–7 days 7 days–30 days
Acute bilirubin encephalopathy	2	Subtle 1 Clonic 0 Tonic 1 Myoclonic 0 Mixed 0	<12 hrs 12–24 hrs 24–72 hrs 72–7 days 2 7 days–30 days

Abbreviation: HIE, hypoxic ischemic encephalopathy.

Table 5 Onset Of Seizure In Neonates With Seizure In Gondar University Comprehensive Specialized Hospital, NICU, 2016–2018 (n=117)

	Total Number (%)	Gestational Age N(%)		
		Preterm	Term	Post Term
<12 hrs	51 (43.6)	1 (1.9)	38 (74.5)	12 (23.6)
12–24 hrs	33 (28.2)	1 (3)	28 (84.8)	4 (12.1)
24–72 hrs	17 (14.5)	1 (5.9)	16 (94.1)	0 (0)
72 hrs–7 days	6(5.1)	0 (0)	6 (100)	0 (0)
7 days–30 days	10 (8.5)	0 (0)	8 (80)	2 (20)
Total	117	3 (2.5)	96 (81)	18 (15.4)

Table 6 Short-Term Outcome In Neonates With Seizure In Gondar University Comprehensive Specialized Hospital, NICU, 2016–2018 (n=117)

Outcome	Sex Of Newborn		Total N (%)
	Male	Female	
Alive with no sequelae	72	12	84 (71.8)
Alive with sequelae	3	7	10 (8.6)
Dead	11	12	23 (19.6)
Total	86	31	117

As compared with neonates with subtle seizure, those with tonic and myoclonic seizures have a higher mortality

rates about 83.6% (OR= 0.164; 95% CI: 0.030, 0.885) and 96% (AOR= 0.040; 95% CI: 0.055, 0.538) respectively.

Discussion

Seizures are the most important clinical manifestation of neurological disorders in the neonatal period. Even though seizures are usually reported to occur more frequently in premature infants,¹¹ in the present study, we observed a predominance of seizures in term newborns with birth weight appropriate to gestational age. These results agree with another studies done by Gacias da Silva et al¹² and Holand M et al.¹³ This finding might be related to regional peculiarities of maternal and birth care or perhaps due to the high incidence of perinatal asphyxia in our cohort, which is a more common cause of seizure in term newborns rather than preterms in whom interventricular hemorrhage and infections are the most frequent causes.¹⁴

In this study, seizure was more common in male neonates as other studies. This could be due to prominent occurrence of opening of the chloride channels, which are excitatory in immature brains, in male brain than females' results in depolarizing the cell perhaps explaining their greater predisposition to seizures.^{15–17}

Perinatal asphyxia, in this study, in agreement with other series, was the most frequent etiology related to neonatal seizures. It is comparable to studies which have shown the

Table 7 A Bivariate And Multivariate Logistic Regression Output Showing Factors Associated With Short-Term Outcomes In Neonates With Seizure GUH, Northwest Ethiopia, 2016–2018 (n=117)

Variable	Short-Term Outcome		COR (95% CI)	AOR (95% CI)	P value For AOR
	Alive	Died			
Parity					
Primipara	56 (84.8%)	10 (15.2%)	1	1	1
Multipara	34 (81.0 %)	8 (19.0%)	0.143 (0.033 to 0.626)	0.172 (0.033 to 0.880)	0.035
Grand multipara	4 (44.4%)	5 (55.6%)	0.188 (0.041 to 0.864)	0.179 (0.032 to 1.005)	0.051
Sex of newborn					
Male	75 (87.2%)	11 (12.8%)	1	1	1
Female	19 (61.3%)	12 (38.7%)	0.232 (0.089 to 0.607)	0.171 (0.055 to 0.538)	0.003
Gestational age in weeks					
<37	13 (33.3%)	2 (66.7%)	1	1	1
37–42	78 (80.4%)	19 (19.6%)	15.000 (0.896 to 251.056)	42.334 (1.326 to 1351.3)	0.034
>42	15 (88.2%)	2 (11.8%)	1.827 (0.385 to 8.679)	2.477 (0.313 to 19.585)	0.390
Seizure type					
Subtle	60 (84.5%)	11 (15.5%)	1	1	1
Tonic	13 (72.2%)	5 (27.8%)	0.321 (0.080 to 1.284)	0.164 (0.030 to 0.885)	0.036
Clonic	14 (93.3%)	1 (6.7%)	0.673 (0.135 to 3.347)	0.479 (0.074 to 3.103)	0.440
Myoclonic	0 (0%)	2 (100%)	0.125 (0.012 to 1.339)	0.040 (0.055 to 0.538)	0.048

incidence from 73.9% to 44%.^{2,15,16,17,18,19¹⁷⁻²¹} neonates with HIE followed by neonates with metabolic abnormalities and intracranial hemorrhage while the main diagnosis in another study was sepsis in 85 (60%) then neonatal encephalopathy in 30 (21%).²⁰ Metabolic abnormalities were found in 42 (47.7%) neonates followed by birth asphyxia representing the second most common cause in his study 14 (15.9%) neonates.⁷ Despite being most common, percentage difference could be because of lack of complete investigation in the study setting due to financial constraints and the high number of term newborns in the study.

In the present study, subtle seizure was found to be the most common type of neonatal seizure accounting for 60.7%, similar results were described in other studies conducted in different settings.^{6,7,21,22} However, these were different from studies in which clonic seizures were the most common.^{20,21} In a study conducted by Soni et al, the commonest type of seizures in term group was tonic seizures which were seen in 15 (37.5%) neonates and subtle seizures in 10 (25%) neonates.²²

The outcome of neonates with seizure in our study, where the mortality rate was 19.6%, is comparable with findings reported by Sahana et al¹⁵ study in which 49.54% of the neonates had recovered completely, 32.11% of the neonates had neurological sequelae, and 18.35% of the neonates died. However, it was higher than that (14.7%) reported in the study of Sabzehei et al.⁶ The difference in the mortality rates from different settings is primarily dependent on the level of the neonatal care and the etiological factors.

Multivariate logistic regression output indicated that sex of newborn and type of seizure was significantly associated with short-term outcomes. As compared with neonates with subtle seizure, those with tonic and myoclonic seizures have higher death rates about 83.6% (OR= 0.164; 95% CI: 0.030, 0.885) and 96% (OR= 0.040; 95% CI: 0.055, 0.538), respectively. This could be associated with the fact that it was associated with meningitis and delayed onset of seizure in HIE which suggests a structural abnormality rather than common metabolic causes.

The main strength of this study is that it is a prospective observational study which is done for the first time in Ethiopia as far as the author's knowledge is concerned. However, it has its limitations. The inclusion of newborns with seizures was based on clinical criteria without synchronized video EEG recording might have resulted in the inclusion of newborns with seizure mimics which have different causes and outcomes. The fact that advanced

neuroimaging studies were not done in the majority of cases due to financial constraints is another major limitation. This study includes short-term follow-up only; further, follow-up is required to evaluate long-term neurological follow-up.

The study revealed subtle seizure was the most common type of neonatal seizure which is common among neonates with asphyxia and metabolic abnormalities. HIE was the commonest etiology of neonatal seizures and in most of the seizures had an onset in the first 72 hrs. Parity, gestational age, neonatal sex, and seizure type were determinants of short-term outcome.

Conclusion

The study revealed subtle seizure was the most common type of neonatal seizure, which is common among neonates with asphyxia and metabolic abnormalities. HIE was the most common etiology of neonatal seizures, which had an onset within the first 72 hrs of what birth. Parity, gestational age, neonatal sex, and seizure type were determinants of mortality of short-term outcome.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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