IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Clinco-etiological Profile and Predictors of Outcome of Neonatal Seizures: A Prospective Observational Study from Egypt

Eman Rateb Abd Almonaem[1*], Ahmed Shaheen Dabour[1], Mona Ahmed Elawady[2], Omima Mohamed Abdel Haie[1]

1. Pediatric Department, Benha Faculty of Medicine, Benha University, Egypt
2. Community Medicine Department, Benha faculty of medicine, Benha University, Egypt

ABSTRACT

Background: Neonatal seizures are the most prevalent neurological disorders. In Egypt, the characteristics and neurodevelopmental outcomes of neonatal seizures have not been sufficiently explored.

Methods: The present study was conducted on 120 full-term and preterm newborns from October 2016 and October 2020. The adverse outcomes of cerebral palsy, mortality, developmental delay, and/or epilepsy have been considered. The associations between adverse outcomes and 13 variables were analyzed.

Results: Hypoxic-ischemic encephalopathy (HIE) (34.2%) was the most common etiology for neonatal seizures, followed by intracranial hemorrhage (25.8%). The predominant seizure type was subtle (57.5%), preceded by clonic seizure (16.7%). Moreover, 72 neonates had a normal outcome, 14 (60%) cases had minor functional disabilities, and 27 (22.5%) newborns survived with one or more neurodevelopmental abnormalities (6 cases had cerebral palsy, and 21 newborns had global developmental delay), with a 17.5 % mortality rate. Based on the univariate analysis, 10 variables were associated with an unfavorable outcome; nonetheless, only three variables, namely metabolic acidosis, abnormal cranial ultrasonography findings, and the presence of congenital heart disease, were independent predictors as illustrated by multivariate logistics.

Conclusion: As evidenced by the obtained results, HIE and intracranial hemorrhage were the most common causes of neonatal seizures. Perinatal insult, prematurity, seizure onset <24 hours, low Apgar score at 1 min, myoclonic or mixed seizure, the efficacy of the anticonvulsant therapy, abnormal cranial U/S, metabolic acidosis, abnormal electroencephalography (EEG) pattern, and the presence of congenital heart disease were the most reliable predictors of adverse outcome.

Keywords: Infants, Neonate, Preterm, Outcome, Seizure

Introduction

Neonatal seizure is an emergency for newborns, and it is essential to identify the etiology and other consequences. Even with better perinatal care, mortality and morbidity in neonatal seizures have remained high. The diagnosis and management of neonatal seizures are encountered with numerous obstacles, emphasizing the need to change the nature of neonatal seizure research (1). Seizures are more widespread during the neonatal period than any other stage of life, with an estimated frequency of roughly three seizures in every 1,000 live births (2). Nevertheless, since their clinical detection is difficult, establishing the present evidence of newborn seizures is problematic.

While seizures are typically the first sign of neurological dysfunction in neonates, their clinical manifestations are disorganized, commonly mild, and extremely diverse at this age (3). Seizures are a potentially fatal condition that can be caused by a wide array of factors. According to the studies performed in numerous

* *Corresponding author*: Eman Rateb Abd Almonaem, Pediatric Department, Benha Faculty Of Medicine, Benha University, Egypt. Tel: 00201224472675; Email: emanrateb79@gmail.com

Please cite this paper as:
Rateb Abd Almonaem E, Shaheen Dabour A, Ahmed Elawady M, Abdel Haie OM. Clinco-etiological Profile and Predictors of Outcome of Neonatal Seizures: A Prospective Observational Study from Egypt. Iranian Journal of Neonatology. 2022 Apr: 13(2). DOI: 10.22038/IJN.2022.60558.2152

low-income countries, the most common etiology is perinatal asphyxia associated with hypoxic-ischemic encephalopathy (HIE) (4). The rare reasons for neonatal seizures include infection, metabolic abnormalities, developmental anomalies, intracranial hemorrhage, and inborn metabolic errors (5). Seizures are one of the most serious neonatal emergencies, necessitating rapid diagnostic and treatment approaches since delayed therapies frequently result in a poor neurological outcome (5). In light of the aforementioned issues, the present study aimed to evaluate the clinical and etiological characteristics of neonatal seizures, as well as their neurodevelopmental outcome, in an Egyptian cohort study.

Methods

Study design and population

This prospective cohort study was conducted from October 2016 to October 2020 in the Neonatal Intensive Care Units (NICUs) at Benha University Hospital (a teaching general hospital, including the Gynecology and Obstetrics Department and NICUs of the Pediatric Department with 40 well-equipped incubators receiving both inborn and outborn admissions) and Benha Children Hospital (a pediatric hospital, including NICUS with 60 well-equipped incubators receiving both inborn and outborn admissions). The Ethics Scientific Committee of the Faculty of Medicine, Benha University, accepted the study protocol in conformity with the World Medical Association's Declaration of Helsinki (6).

Before enrollment in the study, informed consent was obtained from parents/guardians. The inclusion criteria were full-term and preterm neonates <37 weeks [gestational age was estimated by ultrasound and New Ballard Score (NBS)] with clinically apparent neonatal seizures (i.e., within the first 28 days of life fulfilling internationally established criteria for diagnosis). A pediatric neurologist and neonatologist used internationally established criteria to diagnose clinical neonatal seizures (7). Cerebral malformations and genetic disorders were regarded as the exclusion criteria. All patients had at least two years of neurologic follow-up data or at least 1 year if the neonate was normal.

The present study sampled 225 term and preterm newborns, out of whom 120 (53.3%) subjects met the criteria for enrollment. All neonates were subjected to a detailed history, including prenatal history (maternal illness, meconium-stained liquor, and perinatal insults), neonatal history(delivery mode, gender, gestational age, and being small of gestational age), and postnatal history (Apgar score at 1 and 5 minutes, seizure type, seizure onset age, etiology, the efficiency of antiepileptic drugs, elect-roencephalography (EEG) findings, cranial ultrasonography findings, as well as the presence of metabolic acidosis and congenital heart disease).

Maternal illness included premature rupture of membranes, drug abuse, hepatitis B carrier, vaginal group B streptococcus colonization, placenta malfunctions, antepartum hemorrhage, and systemic disease (for example, pre-eclampsia, hypertension, and thyroid disorders). Perinatal insults comprised delayed initial crying, fetal distress, prolonged labor course, the need for resuscitation in the labor room, a cord around the neck, abruptio placentae, and precipitating labor. The onset of seizure was categorized as happening before or after the first 24 hours of life. The Volpe classification scheme was used to classify seizure types (7) depending on paroxysmal symptoms. It included subtle, clonic, myoclonic, tonic, myoclonic, and mixed types.

The clinical history, neuroimaging findings [computed tomography (C.T.) and cranial ultrasonography results], and laboratory testing were performed to determine the primary cause of seizures (cerebrospinal fluid studies, electrolyte levels, lactate, pyruvate, blood gas analysis, serum glucose, alanine, alanine transaminase, and creatine kinase). Certain newborns were screened for congenital infection using rubella, Toxoplasmosis gondii, cytomegalovirus, and herpes simplex virus (TORCH) screening or workup for an inborn error of metabolism. We divided etiology into six distinct categories: (1) HIE (2) transient metabolic disturbances (i.e., hypocalcemia, hypoglycemia, hypomagnesemia, and hyponatremia), (3) infections, (4) intracranial hemorrhage, (5) inborn error of metabolism (i.e., tyrosinemia type 1, isovaleric acidemia, and maple syrup urine disease), (6) and miscellaneous (e.g., neonatal abstinence syndrome), and intrapartum asphyxia necessitated an Apgar score of 6 at 5 minutes and fetal distress.

Confirmatory laboratory evidence of infection (viral or bacterial) was obtained via Cerebrospinal fluid (CSF) or blood culture. Intracranial hemorrhage included subarachnoid, epidural, parenchymal, subdural, and/or intraventricular hemorrhage. Newborns were classified as having an " unknown etiology " if this rigorous diagnostic screening revealed no cause. In tolerated neonates, interictal EEG recordings (international 10-20 system, modified) were made (Medelec, Oxford, England). The neurophysiologists used

visual pattern recognition to scan the EEG for background patterns and seizure action.

The EEG data were divided into two categories: (1) normal background activity and (2) epileptiform or aberrant background activity. Serial cranial ultrasonography tests were performed on almost all infants. Several neonates possessed at least one additional imaging modality, such as cranial C.T. The findings of cranial ultrasonography were categorized into two types: (1) normal and (2) abnormal (i.e., hemorrhage, subependymal, parenchymal echodensities, as well as choroid plexus cysts, brain malformations, and ventricular dilatation).

The first line of treatment was phenobarbital at a loading dose of 20-40 mg/kg and a maintaining dose of 3–8 mg/kg/day intravenously. If the seizures persisted or recurred, we administered phenytoin at a loading dose of 20 mg/kg and a maintenance dose of 4-8 mg/kg/day intravenously. The third line of treatment was levetiracetam at a loading dose of 40 mg/kg divided into two doses and a maintenance dose of 40-60 mg/kg/day intravenously. Metabolic acidosis was characterized as pH<7.35, HCO3<18 mEq/L, and a need for NaHCO3 supplementation. The following data analysis included the neurologic outcome documented at the last follow-up. The following outcomes were defined as follows:

1. Normal and mild neurologic abnormalities (e.g., mild mental retardation, hearing impairment, and motor and/or speech delay relative to age).

2. Cerebral palsy was established as an early-onset, static, and non-progressive motor disability characterized by objective changes in muscular strength, tone, aberrant deep tendon reflexes, posture, and motor skills. The neuromotor examination was conducted in accordance with Levine's clinical criteria(8). Motor skills were compared to those predicted by children of the same age.

3. Global developmental delay was regarded as the major delay in at least two developmental domains: personal-social, gross or fine motor, cognition, speech and language, and daily living activities.

4. Epilepsy was described as repeated unprovoked seizures that needed the use of antiepileptic medications.

5. We classified the four categories indicated previously as follows: "good outcome" (normal and mild neurological abnormalities) and "adverse outcome" (global developmental delay, cerebral palsy, and death).

Statistical Analysis

The collected data were tabulated and analyzed using the SPSS statistical software (version 16). Categorical data were presented as numbers and percentages and were compared using the Chi-square (X2) or Fisher's exact (FET) tests, with a P-value greater than 0.05 implying normality. Using previously identified indicators, univariate and multiple logistic regression models were used to predict unfavorable neurodevelopmental outcomes. The acceptable significance level in this experiment was 0.05 (a p-value less than 0.05 was considered significant).

Results

This prospective cohort study was conducted on 120 neonates (75 males and 45 females) with a mean gestational age of 34.6±3.29 weeks (29-41weeks). A number of 69 newborns were preterm and 41 cases were full-term, and the mean birth weight was 2.2±0.75 kg (0.96-3.8 kg). Moreover, 23 neonates were small for gestational age, and 97 cases were appropriate for gestational age. In terms of delivery mode, 22 (18.3%) and 98 (81.7%) neonates were born by vaginal delivery and cesarean section, respectively. The EEG pattern was normal in 36.7% of studied neonates and abnormal in 63.3% of them, while congenital heart diseases were detected in 12.5% of newborns (Table 1).

Table 1. Characteristics of the studied neonates

	Range	Mean ±SD
Gestational age (weeks)	29-41	34.6± 3.2
Birth weight (kg)	0.96-3.8	2.2±0.75
	No	%
Mode of delivery		
Vaginal delivery	22	18.3
Cesarean section	98	81.7
Gender		
Male	75	62.5
Female	45	37.5
EEG pattern		
Normal	44	36.7
Abnormal	76	63.3
Congenital heart diseases		
Present	15	12.5
Absent	105	87.5
Gestational age		
PT	79	65.8
FT	41	34.2
Weight for gestation		
SGA	23	19.2
AGA	97	80.8

Data were represented as mean±SD or number (percentage).
PT: preterm, FT: full term, SGA: small for gestational age, AGA: appropriate for gestational age

Table 2. Outcome of neonatal seizure patients by primary etiology and predominant seizure type

	N (%)	Overall outcome, n (%)			Abnormal outcome, n (%)		
		Normal	Abnormal	Dead	CP	GDD	Epilepsy
Etiology	120 (100)	72 (60)	27 (22.5)	21 (17.5)	6 (22.2)	21(77.7)	23 (23.2)*
Hypoxic ischemic encephalopathy	41 (34.2)	18 (43.9)	15 (36.6)	8 (19.5)	6 (100)	9 (42.9)	15 (60)*
Intracranial hemorrhage	31 (25.8)	20 (64.5)	6 (19.4)	5 (16.1)	0 (0)	6 (28.6)	4 (16)*
Infection	18 (15)	10 (55.6)	6 (33.3)	2 (11.1)	0 (0)	6 (28.6)	2 (8)
Inborn error of metabolism	4 (3.3)	2 (50)	0 (0)	2 (50)	0 (0)	0 (0)	0 (0)
Transient metabolic disturbance	14 (11.7)	14 (100)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8)*
Miscellaneous	6(5)	2 (33.3)	0 (0)	4 (66.7)	0 (0)	0 (0)	0 (0)
Unknown etiology	6(5)	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
		Clinical type of seizure					
Subtle	69 (57.5)	46 (66.7)	18 (26.1)	5 (7.2)	3 (50)	15 (71.4)	10 (43.5)*
Clonic	20 (16.7)	15 (75)	3 (15)	2 (10)	3 (50)	0 (0)	4 (17.4)
Tonic	12 (10)	8 (66.7)	4 (33.3)	0 (0)	0 (0)	4 (33.3)	2 (8.6)
Myoclonic	3 (2.5)	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	4 (17.4)
Mixed	16 (13.3)	3 (18.8)	2 (12.5)	11(68.8)	0 (0)	2 (9.5)	3 (13.1)
Percentage of 99 survivals							
*:sig							

Data represented as number (percentage)
CP: cerebral palsy; GDD: global developmental delay

Out of the 120 neonates, 64 cases had a normal outcome, 8 (60%) newborns had a minor functional disability, 27 (22.5%) subjects survived with neurodevelopmental abnormalities, and 21 (17.5%) neonates died. Cerebral palsy was diagnosed in 6 (22.2%) abnormal survivors, and 22 (77.7 %) neonates had global developmental delay. Out of 99 patients who survived after their first discharge, epilepsy was diagnosed in 23 (23.2 %) cases. The most common etiology was HIE which was detected in 41 (34.2%) neonates, followed by intracranial hemorrhage which was identified in 31(25.8%) cases. The most common cause of mortality (19.5%) was HIE. The most prevalent type of seizure was subtle, accounting for 57.5% of all seizures; moreover, this kind exhibited the strongest association with epilepsy (43.5%)(Table 2).

Both the 1-minute and 5-minute Apgar scores were substantially related to an adverse outcome (P<0.001 each). Moreover, 26 (21.7%), 45(37.4%), 26 (21.7%), and 23 (19.2 %) neonates experienced seizures within 24 hours, between 24 and 72 hours, between 3 and 7 days, and beyond the first 7 days of life, respectively. Moreover, 62 (51.7%) newborns needed monotherapy with phenobarbital to achieve clinical seizure control. Additional antiepileptic medications were administered to 58 (48.3%) neonates whose seizures could not be controlled with phenobarbital alone [phenytoin (36) or phenytoin and levetiracetam (22)](Table 3).

The following 10 poor outcome predictors were found by univariate analysis: prematurity (OR=0.3; 95% CI: 0.12-0.79), perinatal insults (OR=8.31; 95% CI: 2.7-25.6), low Apgar score at

Table 3. Outcomes of neonatal seizures in different clinical conditions

Variable	Total (n)	Normal outcome	Adverse outcome	X2 test	P-value
Perinatal insults					
Yes	85	41(48.2%)	44 (51.8%)	16.8	<0.001** (HS)
No	35	31(43.1%)	4 (8.3%)		
Apgar score at 1 min.					
0-3	24	1 (4.2%)	23 (95.8%)	43.2	<0.001** (HS)
4-6	67	45 (67.2%)	22 (32.8%)		
7-10	29	26 (89.7%)	3 (10.3%)		
Apgar score at 5 min.					
0-3	-	—	—	17.3	<0.001** (HS)
4-6	12	0 (0%)	12 (100%)		
7-10	108	72 (66.7%)	36 (33.3%)		
Seizer onset					
<24 h	26	7 (9.7%)	19 (39.6%)	15.1	<0.001** (HS)
>24 h	94	65 (90.3%)	29 (60.4%)		

Table 3. Continued

Medications					
Phenobarbital	62	61(98.4%)	1(1.6%)	78.96	<0.001** (HS)
Phenobarbital+ phenytoin	36	6 (16.7%)	30 (83.3%)		
Phenobarbital+ phenytoin+ levetiracetam	22	5 (22.7%)	17 (77.3%)		
Metabolic acidosis					
Absent	63	58 (92.1%)	5 (7.9%)	56.8	<0.001** (HS)
Present	57	14 (24.6%)	43 (75.4%)		
Cranial US					
Normal	47	41 (87.2%)	6 (12.8%)	23.8	<0.001** (HS)
Abnormal	73	31 (42.5%)	42 (57.5%)		
EEG findings					
Normal	44	32 (72.7%)	12 (27.3%)	4.68	0.03* (S)
Abnormal	76	40 (52.6%)	36 (47.4%)		
Seizure type					
Subtle	69	49 (71.0)	20 (29.0)	9.99	0.04* (S)
Clonic	20	16 (80.0)	4 (20.0)		
Tonic	12	6 (50.0)	6 (50.0)		
Myoclonic	3	0 (0.0)	3 (100)		
Mixed	16	6 (37.5)	10 (62.5)		
Congenital heart diseases					
Present	15	1 (6.7)	14 (93.3)	40.5	<0.001** (HS)
Absent	105	90 (85.7)	15 (14.3)		
Gestational age					
PT	79	21 (26.6)	58 (73.4)	15.4	<0.001** (HS)
FT	41	26 (63.4)	15 (36.6)		
Weight for gestation					
SGA	23	12 (52.2)	11(47.8)	0.003	0.96
AGA	97	50 (51.5)	47(48.5)		
Delivery					
Spontaneous vaginal	22	10 (45.5)	12 (54.5)	0.09	0.77
CS	98	48(49.0)	50 (51.0)		

Data represented as number (percentage).
PT: preterm, FT: full term, SGA: small for gestational age, AGA: appropriate for gestational age, CS: cesarean section
*: significant (P≤ 0.05 was considered)
**: highly significant (P<0.001 was considered)

1 min (OR=47; 95% CI: 5.9-371.3), seizure onset less than 24 hours (OR=5.3; 95% CI: 1.39-20.7), seizure type (OR=0.164; 95% CI: 0.03-0.885 for myoclonus and OR= 0.04; 95% CI: 0.055-0.538 for mixed type), efficacy of anticonvulsant therapy (OR=0.171; 95% CI: 0.055-0.538), metabolic acidosis(OR=35.6; 95% CI: 11.9-106.4), cranial ultrasound abnormality (OR=9.25; 95% CI: 3.49-24.52), abnormal EEG findings (OR= .4; 95% CI: 1.07-5.35), and the presence of congenital heart diseases (OR=0.198; 95% CI: 0.06-0.66).

Furthermore, four poor outcome predictors were detected by multivariate analysis, including the presence of metabolic acidosis (OR=3.057; 95% CI: 1.062 - 8.331), abnormal cranial ultrasound (OR=3.470; 95% CI: 1.567-7.639), abnormal EEG findings (OR=4.53; 95% CI: 1.358 – 15.13), and the presence of congenital heart diseases (OR= 5.3; 95% CI: 1.39-20.7)(Table 4).

Table 4. Predictors of adverse outcomes in neonatal seizures

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	P-value
Perinatal insults				
No (35)	1.000			0.313
Yes (85)	8.31(2.7-25.6)	<0.001**	-	
Apgar score at 1 min.				
7-10 (29)	1.000			
4-6 (67)	199.3 (19.3-2052.1)	<0.001**	-	0.998
0-3 (24)	47.0(5.9 -371.3)	<0.001**	-	0.998

Table 4. Continued

Apgar score at 5 min.				
7-10 (108)	1.000			
4-6 (12)	2.84(0.95-6.32)	0.998	-	1.000
0-3 (0)	NA			
Seizer onset				
>24 h (94)	1.000			0.999
<24 h (26)	0.164(0.06-0.43)	<0.001**		
Medications				
No medications (0)	1.000			
Phenobarbital (62)	0.172(0.033-0.880)	0.035*	-	0.994
Phenobarbital + AED(58)	0.171(0.055 - 0.538)	0.003**	-	0.991
Metabolic acidosis				
Absent (63)	1.000			
Present(57)	35.6(11.9-106.4)	<0.001**	3.057(1.062 - 8.331)	<0.001**
Cranial US				
Normal (47)	1.000			
Abnormal(73)	9.25(3.49-24.52)	<0.001**	3.470 (1.567 - 7.639)	0.043*
EEG pattern				
Normal (44)	1.000		-	0.09
Abnormal(76)	2.4(1.07-5.35)	0.032*		
Seizure type				
Subtle (69)	1.000		-	
Clonic (20)	2.477(0.313- 19.58)	0.390	-	
Tonic (12)	0.479(0.074 -3.103)	0.440		
Myoclonic (3)	0.164(0.030- 0.885)	0.036*	-	0.446
Mixed (16)	0.040(0.055 -0.538)	0.048*	-	
Congenital heart diseases				
Presen t(15)	0.198(0.06-0.66)	0.009**	5.3(1.39-20.7)	0.015**
Absent(105)	1.000			
Gestational age				
PT (79)	0.30(0.12-0.79)	0.015**	-	0.42
FT(41)	1.000			
Weight for gestation				
SGA (23)	0.67(0.26-1.68)	0.396	-	0.74
AGA(97)	1.000			
Delivery				
Spontaneous vaginal (22)	1.000		-	0.07
CS(98)	0.68 (0.31-1.5)	0.34		

AED: anti-epileptic drugs; PT: preterm, FT: full term, SGA: small for gestational age, AGA: appropriate for gestational age, CS: cesarean section.
*: significant (P≤ 0.05 was considered)
**: highly significant (P<0.001 was considered)

Discussion

The overwhelming majority of seizures (95%) in the study population were symptomatic of an identified etiology from a wide variety of causes. The proportion of newborns with unknown causes was much lower than that in earlier studies (5%) (5,9). Moreover, there were significant differences in the proportional prevalence of seizures among etiologic categories (5,9,10,11). Although the prevalence has differed, HIE has been the predominant cause of neonatal seizures in most prior studies, almost certainly due to the inconsistency of the diagnostic criteria employed.

In the present study, HIE continued to be the most common cause of seizures (34.2%), accompanied by intracranial hemorrhage (25.8%), infection (15%), transient metabolic disturbances (15%), miscellaneous (5%), and inborn metabolic errors (3.3%). Moreover, in six newborns, the cause was unknown (5%). The findings of this study were in agreement with those reported by Nunes et al. who referred to HIE as the most prevalent cause (51%), accompanied by transient metabolic disturbances (14%), infection (congenital, septicemia, bacterial meningitis (9%), intraventricular hemorrhage (6%), venous

infarction (3%), inborn metabolic error (3%), and cerebral dysgenesis (2%). (12).

In a similar vein, in their prospective cohort study, Baudou et al. (13) reported the prevalence of each of the preceding etiologies of neonatal seizures: ischemic infarction: 13%, intracranial infections: 8%, metabolic or electrolyte disorder: 3%, inborn metabolic errors: 2%, co-morbidity: 5%, HIE: 37%, and intracranial hemorrhage: 15%. The etiology was unidentified in 16 cases. In the current research, 25.8% of newborns' intracranial hemorrhage was similar to the study by Heljic et al. (10) who pointed to an increase in intraventricular hemorrhage prevalence (30%) in the cohort study, consisting of 33 and 67 preterm and full-term newborns, respectively. The rising prevalence of intracranial hemorrhage may be related to the inclusion of 79 preterm newborns in the present study.

The current research pointed out that the most frequent seizure type was subtle (57.5%), accompanied by clonic (16.7%), mixed (13.3%), tonic (10%), and myoclonic (2.5%). The results of this study were in line with those reported by Sabzehei et al. (5) who identified mild seizures (38.2%), accompanied by tonics (29.4%), clonic (26.4%), and myoclonic as the most common forms in their study (5.9%). Nevertheless, Kumar et al. (3) revealed that multifocal clonic seizures (42.24%) were the most prevalent form of seizure, followed by myoclonic seizures (0.86%), widespread tonic seizures (21.55%), subtle seizures (8.19%), and focal clonic seizures (6.47%).

Mortality was 17.5 % in this research, compared to 9%-15% in prior studies (2). According to Padiyar et al. (14), neonatal seizures were correlated with a mortality rate of 3.3%-39.4%, with an average mortality rate of 4%. At 39.4%, newborns at or less than 24 weeks gestational age had the highest mortality rate. Scher et al. (15) observed a 58% mortality rate in preterm newborns with verified neonatal seizures on EEG. Ronen et al. (16) examined 26 newborns with neonatal seizures and observed a 42% mortality rate. Along the same lines, Pisani et al. (17) assessed 51 preterm newborns with documented EEG seizures and observed a 34 % mortality rate. The disparities could be attributed to differences in study populations, outcomes, and seizure diagnosis.

Based on the outcome of 120 assessed newborns, 72 (60%) newborns had a normal consequence, 27 (22.5%) neonates survived with a neurodevelopmental dysfunction, 6 (22.2%) cases had cerebral palsy, and 22 (77.7%) neonates had global developmental delay. Moreover, out of 99 newborns who survived after the first discharge, epilepsy was diagnosed in 23 (23.2%) cases, and 21 (17.5%) newborns ended up in death. The findings of this study were in accordance with those obtained by Lai et al. (9) who revealed that out of 232 recruited newborns, 125 cases had a normal outcome, 14 newborns had a minor functional disability (59.9%), 55 (23.7%) subjects survived with one or more neurodevelopmental abnormalities, and 38 (16.4 %) cases died. Out of the 204 neonates who survived beyond their initial discharge, 47 (23.0%) cases had epilepsy.

According to our latest study, the leading cause of mortality was HIE (19.5%), accompanied by cerebral hemorrhage (16.1%). The most common cause of abnormal outcome (36.6%) was HIE, accompanied by cerebral hemorrhage and infection (19.4% and 33.3%). Newborns with transient metabolic disturbances and unknown etiology had the best outcome. The most often encountered etiology of epilepsy was HIE. Out of 99 survived newborns, epilepsy was diagnosed in 23 (23.2%) cases. According to some research, the etiology of newborn seizures is the most critical factor impacting outcome. (1,7,18,19,20). In particular, asphyxia and cerebral hemorrhage are related to poor outcomes. Moreover, poor outcomes were correlated with central nervous system infection, cerebral dysgenesis, and global hypoxia-ischemia (1,21). Neonatologists must have accurate and early predictors of outcome to effectively plan management. The selected variables for this study are readily accessible.

Gestational age, perinatal insult, Apgar score 1 minute, seizure onset <24 hours, anticonvulsant efficacy, metabolic acidosis, cranial U/S abnormality, abnormal EEG pattern, and congenital disease presence were significantly associated with adverse outcomes in this study. Factors of the predictions published in the literature included etiology, type of seizures and early seizure, prolonged and recurring seizure, gestational age, birth weight, Apgar rating at 5 min, resuscitation maneuvers requirements, neurological examination and EEG, and ultrasonographic (USG) findings (22,23,24).

Delivery mode, 5-minute Apgar, and gestation weight were not significantly related to unfavorable outcomes in this study. Term newborns with seizures are more probable to have normal outcomes, as compared to preterm newborns (1,18,25). The majority of experimental

information shows considerable adverse long-term effects of preterm neonatal seizures, such as ongoing learning, memory, and cognition impairments (26,27). Apgar score is a reliable neurological predictor of 5 minutes as opposed to 1 minute (28,29). Lai et al. (9) noted the considerable impact of early neonatal seizures (less than 24 hours) with adverse outcomes. In the same context, Amare et al. (30) demonstrated increased mortality rates in newborns with tonic and myoclonic seizures of around 83.6% (OR=0.164; 95% CI:0.030,885), and 96% (AOR=0.040;95% CI:0.055, 0.538), compared to subtle neonatal seizures.

Some studies reported that neonates with general tonic, myoclonic, and subtle seizures have poor outcomes as opposed to clonic seizures. Nonetheless, recent studies have indicated that the prognostic significance of type seizures cannot be dependable since several types of seizures often coexist in the same patient (22). In their study, Ronen et al. denoted that several automated external defibrillators (AEDs) are necessary to indicate poor outcomes (2). Van der Heide et al. (31) stated that the most striking finding in their study was that failure to achieve seizure control was strongly associated with poor outcomes rather than the number of AEDs required.

Consistent with the findings of the present study, an abnormal EEG background and neuroimaging (USG/CT/MRI) patterns were most predictive of poor outcomes in neonatal seizures (1,32,24,33). While the magnetic resonance imaging (MRI) technique better discovers neurological abnormalities, cranial ultrasonography is sufficiently sensitive to find most abnormalities recognized to be related to poor neurological outcomes (34,35). Cranial ultrasonography is cost-effective and non-invasive, and various studies have already demonstrated its prediction for eventual neurological sequelae (36,37).

Newborns with complex congenital cardiac diseases run a high risk of perioperative seizures (38). It is evident that convulsive conditions lead to elevated systemic and cerebral metabolism, requiring greater energy supplies. Heart diseases can increase the imbalance in energy and lead to adverse outcomes (7). In the present study, the presence of congenital heart disease was a major risk factor for adverse outcomes.

Since this study was a prospective observational cohort study, it had complete records and followed the protocol of our unit for the diagnosis and management of neonatal seizures. Among the notable strengths of the current study, we can refer to the performance of EEG in all neonates with no missed cases and head Ultrasound in the majority of the events. However, we had limitations of small sample size, lack of follow-up of the neonates with EEG abnormalities, absence of video EEG monitoring in cases of abnormal EEG pattern, failure to perform brain MRI in the majority of cases due to financial constraints of low-income countries, and a short-term follow-up period. Further follow-up is required to evaluate long-term neurological outcome.

Conclusion

The results of the present research demonstrated a high mortality rate of neonatal seizures, compared to previous studies. Intracranial hemorrhage and HIE were the most common causes in preterm and term neonates, respectively. Prematurity, perinatal insult, low Apgar score at 1 min, seizure onset within <24 hours, myoclonic or mixed seizure, anticonvulsant efficacy, metabolic acidosis, cranial U/S abnormality, abnormal EEG pattern, and the presence of congenital heart disease were the most reliable predictors of adverse outcomes.

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding

The authors did not receive any source(s) of support in the form of grants.

Authors' contributions

Eman R. Abd Almonaem: designed the study, analyzed data, and drafted the manuscript; Ahmed Shaheen Dabour: Collected the data and helped in data analysis; Mona Ahmed Elawady: analyzed data and drafted the manuscript; Omima Mohamed Abdel Haie: collected data and analyzed data.

References

1. Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, Stewart J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics. 2006;117(4):1270–80.
2. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures:

a population-based study. Neurology. 2007; 69(19):1816–22.
3. Kumar A, Gupta A, Talukdar B. Clinico-etiological and EEG profile of neonatal seizures. Indian J Pediatr. 2007;74(1):33–7.
4. Talebian A, Jahangiri M, Rabiee M, Masoudi Alavi N, Akbari H, Sadat Z. The Etiology and Clinical Evaluations of Neonatal Seizures in Kashan, IRAN. Iran J child Neurol. 2015;9(2):29–35.
5. Sabzehei MK, Basiri B, Bazmamoun H. The Etiology, Clinical Type, and Short Outcome of Seizures in Newborns Hospitalized in Besat Hospital/ Hamadan/ Iran. Iran J child Neurol. 2014;8(2):24–8.
6. Puri KS, Suresh KR, Gogtay NJ, Thatte UM. Declaration of Helsinki, 2008: implications for stakeholders in research. J Postgrad Med. 2009;55(2):131–4.
7. Volpe JJ. Neurology of the newborn. Philadelphia: Saunders/Elsevier; 2008. Available at: http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-B9781416039952X1000X
8. Levine MS. Cerebral palsy diagnosis in children over age 1 year: standard criteria. Arch Phys Med Rehabil. 1980;61(9):385–9.
9. Lai Y-H, Ho C-S, Chiu N-C, Tseng C-F, Huang Y-L. Prognostic factors of developmental outcome in neonatal seizures in term infants. Pediatr Neonatol. 2013;54(3):166–72.
10. Heljic S, Uzicanin S, Catibusic F, Zubcevic S. Predictors of Mortality in Neonates with Seizures; a Prospective Cohort Study. Med Arch. 2016; 70(3):182–5.
11. Bagla J, Garg H, Gulati RK, Gupta PP. Clinicoetiology Profile of Neonatal Seizures in Tertiary Care Level Ii Neonatal Intensive Care Unit. Indian J Child Health. 2017;04(03):383–6.
12. Nunes ML, Martins MP, Barea BM, Wainberg RC, Costa JC da. Neurological outcome of newborns with neonatal seizures: a cohort study in a tertiary university hospital. Arq Neuropsiquiatr. 2008;66(2A):168–74.
13. Baudou E, Cances C, Dimeglio C, Hachon Lecamus C. Etiology of neonatal seizures and maintenance therapy use: a 10-year retrospective study at Toulouse Children's hospital. BMC Pediatr. 2019;19(1):136.
14. Padiyar S, Nusairat L, Kadri A, Abu-Shaweesh J, Aly H. Neonatal seizures in the U.S. National Inpatient Population: Prevalence and outcomes. Pediatr Neonatol. 2020;61(3):300–5.
15. Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. Pediatrics. 1993 ;91(1):128–34.
16. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. J Pediatr. 1999;134(1):71–5.
17. Pisani F, Barilli AL, Sisti L, Bevilacqua G, Seri S. Preterm infants with video-EEG confirmed seizures: outcome at 30 months of age. Brain Dev. 2008;30(1):20–30.
18. Holden KR, Mellits ED, Freeman JM. Neonatal seizures. I. Correlation of prenatal and perinatal events with outcomes. Pediatrics. 1982;70(2):165–76.
19. Mellits ED, Holden KR, Freeman JM. Neonatal seizures. II. A multivariate analysis of factors associated with outcome. Pediatrics. 1982; 70(2):177–85.
20. Scher MS. Neonatal seizures and brain damage. Pediatr Neurol. 2003 ;29(5):381–90.
21. Hall RT, Hall FK, Daily DK. High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. J Pediatr. 1998;132(2):345–8.
22. Pisani F, Sisti L, Seri S. A scoring system for early prognostic assessment after neonatal seizures. Pediatrics. 2009;124(4):e580-7.
23. Pisani F, Leali L, Parmigiani S, Squarcia A, Tanzi S, Volante E, et al. Neonatal seizures in preterm infants: clinical outcome and relationship with subsequent epilepsy. J Matern neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2004;16 Suppl 2:51–3.
24. Garfinkle J, Shevell MI. Prognostic factors and development of a scoring system for outcome of neonatal seizures in term infants. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc. 2011;15(3):222–9.
25. Ellison PH, Largent JA, Bahr JP. A scoring system to predict outcome following neonatal seizures. J Pediatr. 1981;99(3):455–9.
26. Sayin U, Sutula TP, Stafstrom CE. Seizures in the developing brain cause adverse long-term effects on spatial learning and anxiety. Epilepsia. 2004;45(12):1539–48.
27. Cornejo BJ, Mesches MH, Coultrap S, Browning MD, Benke TA. A single episode of neonatal seizures permanently alters glutamatergic synapses. Ann Neurol. 2007;61(5):411–26.
28. Garfinkle J, Shevell MI. Predictors of outcome in term infants with neonatal seizures subsequent to intrapartum asphyxia. J Child Neurol. 2011; 26(4):453–9.
29. Gebremariam A, Gutema Y, Leuel A, Fekadu H. Early-onset neonatal seizures: types, risk factors and short-term outcome. Ann Trop Paediatr. 2006;26(2):127–31.
30. Amare HT, Amare AT. Etiology, Clinical Features, And Short-Term Outcome Of Seizures In Newborns Admitted To The University Of Gondar Hospital, Ethiopia. Pediatr Heal Med Ther. 2019;10:107–13.
31. van der Heide MJ, Roze E, van der Veere CN, Ter Horst HJ, Brouwer OF, Bos AF. Long-term neurological outcome of term-born children treated with two or more anti-epileptic drugs during the neonatal period. Early Hum Dev. 2012;88(1):33–8.
32. Silverstein FS, Jensen FE. Neonatal seizures. Ann Neurol. 2007;62(2):112–20.
33. McBride MC, Laroia N, Guillet R. Electrographic

seizures in neonates correlate with poor neuro-developmental outcome. Neurology. 2000;55(4): 506–13.
34. Leijser LM, de Bruïne FT, Steggerda SJ, van der Grond J, Walther FJ, van Wezel-Meijler G. Brain imaging findings in very preterm infants throughout the neonatal period: part I. Incidences and evolution of lesions, comparison between ultrasound and MRI. Early Hum Dev. 2009; 85(2):101–9.
35. Leijser LM, Steggerda SJ, de Bruïne FT, van der Grond J, Walther FJ, van Wezel-Meijler G. Brain imaging findings in very preterm infants throughout the neonatal period: part II. Relation with perinatal clinical data. Early Hum Dev. 2009;85(2):111–5.
36. Leijser LM, de Vries LS, Cowan FM. Using cerebral ultrasound effectively in the newborn infant. Early Hum Dev. 2006 Dec;82(12):827–35.
37. Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2002;58(12): 1726–38.
38. Clancy RR, Sharif U, Ichord R, Spray TL, Nicolson S, Tabbutt S, et al. Electrographic neonatal seizures after infant heart surgery. Epilepsia. 2005; 46(1):84–90.