The Egyptian Journal of Hospital Medicine (July 2024) Vol. 96, Page 3134-3141

Assessment of Outcome and Prognosis among Neonatal Seizure Patients

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ABSTRACT

Background: Paroxysmal changes in neuronal functioning characterize neonatal seizures. In order to diagnose brain damage, serial ultrasonography is crucial.

Objective: To assessment of characteristics, lines of management and outcome among neonatal seizure patients.

Subjects and methods: Sixty neonatal patients with neonatal seizures who were admitted to the neonatal intensive care unit (NICU) at Abul-Reesh and Kasr EL Aini Hospital before or after 28 days of age underwent electroencephalograms (EEGs), cranial ultrasounds, and other laboratory tests as part of this prospective study.

Result: Myoclonic seizures accounted for 22 cases (36.7% of all seizures), followed by mixed types (17 cases, 28.3% of all seizures), subtle types (10 cases, 16.7% of all seizures), and clonic and tonic seizures (8.3% of all seizures) respectively. There was just one infant who experienced a multifocal clonic seizure. 40% of seizures were caused by hypoxic-ischemic encephalopathy, 17% by sepsis, 13% by intraventricular hemorrhage and hypocalcemia, 7% by cerebral hemorrhage, 5% by kernicterus, 3% by metabolic abnormalities, and 2% by meningitis. Myoclonic seizures were associated with poor outcome (death in 59.1%) whereas most of cases with mixed and subtle types were discharged in ratios of (70.6%) and (90%) respectively, however all cases with tonic and multifocal clonic seizures died. We observed poor outcome among the polytherapy use of certain anticonvulsant drugs especially levetiracetam, lamotrigine, and midazolam.

Conclusion: While the prognosis is dismal for seizures that have persisted for a long period, it improves when neonatal seizures are controlled early on. It is possible to detect mild to moderate brain lesions using a combination of neuro-imaging and newborn EEG.

Keywords: Outcome, Prognosis, Neonatal Seizure.

INTRODUCTION

Neonatal seizures are a common neurological emergency affecting approximately 1–3% of newborns [1,2]. They are defined as abnormal, spontaneous, and excessive electrical discharges in the brain, manifesting as various clinical presentations [3]. These seizures can vary in severity and duration, ranging from subtle and brief to prolonged and dramatic. Types of neonatal seizures include clonic seizures, which involve rhythmic jerking movements of the limbs, trunk, or face; tonic seizures, characterized by sustained stiffening of muscles; myoclonic seizures, which are brief, shock-like muscle contractions; atonic seizures, resulting in sudden loss of muscle tone; apneic seizures, where breathing ceases; and subtle seizures, which present as subtle changes in behavior, such as eye movements, facial grimacing, or sucking movements [4].

Neonatal seizures are often caused by underlying brain injuries or abnormalities, which can occur before, during, or after birth. Common causes include hypoxic-ischemic encephalopathy, brain damage due to lack of oxygen during delivery; infections such as meningitis, encephalitis, or congenital infections (e.g., cytomegalovirus, rubella); metabolic disorders like hypoglycemia, hypocalcemia, or hypomagnesemia; withdrawal syndromes from drugs like heroin or alcohol; genetic disorders including cerebral malformations or genetic epilepsies; and brain hemorrhage, intracranial bleeding that can be caused by a variety of factors, such as premature birth, trauma, or clotting disorders [3].

Diagnosing neonatal seizures can be challenging due to the wide range of clinical presentations. Careful observation, detailed history, and electroencephalogram (EEG) monitoring are crucial for confirmation [1,2]. Treatment focuses on managing the underlying cause and preventing further seizures. Supportive care, such as maintaining adequate oxygenation, blood sugar, and electrolytes, is crucial. Anticonvulsant medications, including phenobarbital, phenytoin, and diazepam, are common choices. Exchange transfusion may be necessary for severe hyperbilirubinemia-related seizures [3].

The outcome of neonatal seizures varies greatly depending on the underlying cause, severity, and duration of the seizures. While some infants may experience a full recovery, others may develop long-term neurological deficits such as cerebral palsy, intellectual disability, or epilepsy [1,2]. Early diagnosis and prompt treatment are crucial for optimizing outcomes. Prognosis is heavily influenced by the underlying cause: Prompt treatment for infections can often lead to complete recovery, while outcome for hypoxic-ischemic encephalopathy can vary significantly based on the severity of brain damage. Prognosis for genetic disorders may depend on the specific genetic condition [3].

Prompt recognition and management of neonatal seizures are critical for minimizing the risk of long-term neurological complications [1,2]. Early diagnosis and treatment can help to control seizures, manage the underlying cause, and improve the chances

Received: 25/03/2024
Accepted: 25/05/2024

of a good outcome [3]. Careful observation for seizure activity and regular neurological examinations are crucial. Electroencephalogram (EEG) testing can help confirm the diagnosis and identify the location and type of seizure activity. Prompt initiation of appropriate treatment, including supportive care and anticonvulsant medications, is essential for preventing further seizures and minimizing brain damage [2].

Objectives: To assessment of characteristics, lines of management and outcome among neonatal seizure patients.

PATIENTS AND METHODS

Sixty neonatal patients with neonatal seizures who were admitted to the neonatal intensive care unit (NICU) at Abul-Reesh and Kasr EL Aini Hospitals before or after 28 days of age underwent electroencephalograms (EEGs), cranial ultrasounds, and other laboratory tests as part of this prospective study from May 2014 to May 2015.

Inclusion Criteria: Seizures in any neonate, whether full-term (>37 weeks) or preterm, are a serious health concern.

Exclusion Criteria: Symptoms such as restlessness and other signs that resemble seizures in newborns and benign neonatal sleep myoclonus.

METHODS

All babies were subjected to:

I- Complete history taking: Factors such as age, the presence or absence of certain medical conditions (such as diabetes mellitus, high blood pressure, thyroid issues, kidney disease, urinary tract infections (UTIs) , cardiology, pulmonary illness, and hematology), and the medications taken.

Neonatal history: Gestational age, sex, birth weight, mode of delivery, full anthropometric measurement, prenatal risk factors, assessment of seizure type, length, age of onset and frequency, newborn sickness, oxygen supply, feeding, and medications.

Family history: Inquiring about a family history of problems such as abortion or death, as well as consanguinity or having a sister with a newborn seizure or a comparable situation.

II- General Examination: Every patient had a thorough physical examination.

III- Systemic examinations: Chest examination and cardiac examination. Followed by echocardiography scan**,** abdominal examination, and neurological examination.

Neurological examination:

Within one day of birth, all neonates underwent a standardized neurologic evaluation. Throughout their stay, they had a battery of neurological tests to rule out hypoxic ischemic encephalopathy. These tests included checks for seizures (kind and duration), muscle tone, and newborn reflexes.

IV- Laboratory investigation:

A full blood count, C-reactive protein, arterial blood gases, cerebrospinal fluid (CSF) for signs of infection, serum electrolytes (calcium, salt, magnesium, potassium, and phosphorus), and blood glucose were the first line of examination in all neonates.

Based on their medical history, physical exam findings, and the results of any necessary tests, neonates suspected of having a metabolic disorder underwent further testing, including blood cultures, serum urea/creatinine, liver function tests, ammonia, lactate, organic acid profiles, ketones in urine, tandem mass spectrometry, and more.

Cranial ultrasound (CUS):

A portable sectorial ultrasound machine (Siemens/Adara Somoline) with a transducer of (5 and 7.5) MHZ was used to acquire standard coronal, sagittal, and para-sagittal images during at least one imaging examination that was conducted during the neonatal period in order to screen for major cranial U.S. lesions.

Electroencephalogram (EEG):

A digital electroencephalogram (EEG) machine (Nihon Kohden 910 A, China) was used for the recording, which lasted between five and ten minutes. The international 10/20 system, which has been modified, was used for the placement of cerebral electrodes. Electrodes were placed in several configurations to cover 11 different areas of the brain using bipolar and unipolar channels. These electrodes were placed in the following locations: frontal, central, parietal, and occipital midline, as well as the left and right frontopolar, temporal, and occipital midline. A skilled electroencephalographer examined the EEG.

Ethical approval:

The Ethics Committee of the Faculty of Medicine at Abul-Reesh and Kasr EL Aini Hospitals approved the study. Parents provided written informed consent before participating in the study, after being told about the study's goals, process, and relevant objectives. The Helsinki Declaration was followed at all stages of the inquiry.

Statistical analysis

Software developed by SPSS Inc. of Chicago, Illinois, USA, specifically for Windows, version 25.0, was used to analyze all of the data. Categorical data were presented as frequency and percentage and were compared by Chi-square or Fisher's exact test. P-value < 0.05 was considered significant.

RESULTS

The mean birth weight of the infants in this study was 2,748 grams, and half of them were born via vaginal delivery. Of the infants in this group, 53.3% were males.

On top of that, 35 neonates (58.3%) made it through the ordeal, whereas 25 (41.7%) did not. The study found that half of the patients experienced perinatal hypoxia, which was confirmed by a history of protracted or artificial labor, and that 46.7% of the kids were born with sepsis. Out of 60 kids in the study, 36 were born at full term (60%). In terms of weight, 36 infants (or 60%) weighed more than 2500 grams (Table 1).

Table (1): Demographics of neonatal cases (n=60)

Variables		Count	Column N %
Sex	Male	32	53.3%
	Females	28	46.7%
Weight	>2.5 kg	36	60 %
	<= 2.5kg	24	40 %
Gestational age	Full term	36	60.0%
	Post Term > 40 weeks	7	11.7%
	Preterm < 35 weeks	17	28.3%

Nineteen percent of the moms reported having lost prior babies during the neonatal period, and ten percent reported having an abortion in the past. One infant, accounting for 1.7% of the total, had a confirmed history of newborn seizures in their family. The 60 cases included 13 infants born from consanguineous marriages, accounting for 21.6% of the total.

Myoclonic seizures accounted for 22 cases (36.7% of all seizures), followed by mixed types (17 cases, 28.3% of all seizures), subtle types (10 cases, 16.7% of all seizures), and clonic and tonic seizures (8.3% of all seizures) respectively. There was just one infant who experienced a multifocal clonic seizure. The duration of seizures in the neonates included in this study varied, with 43 (71.7%) experiencing seizures for less than three minutes and 17 (28.3%) for more than three minutes.

In our study hypoxic ischemic encephalopathy was the commonest cause of seizures as 40% followed by sepsis 17% (Figure 1).

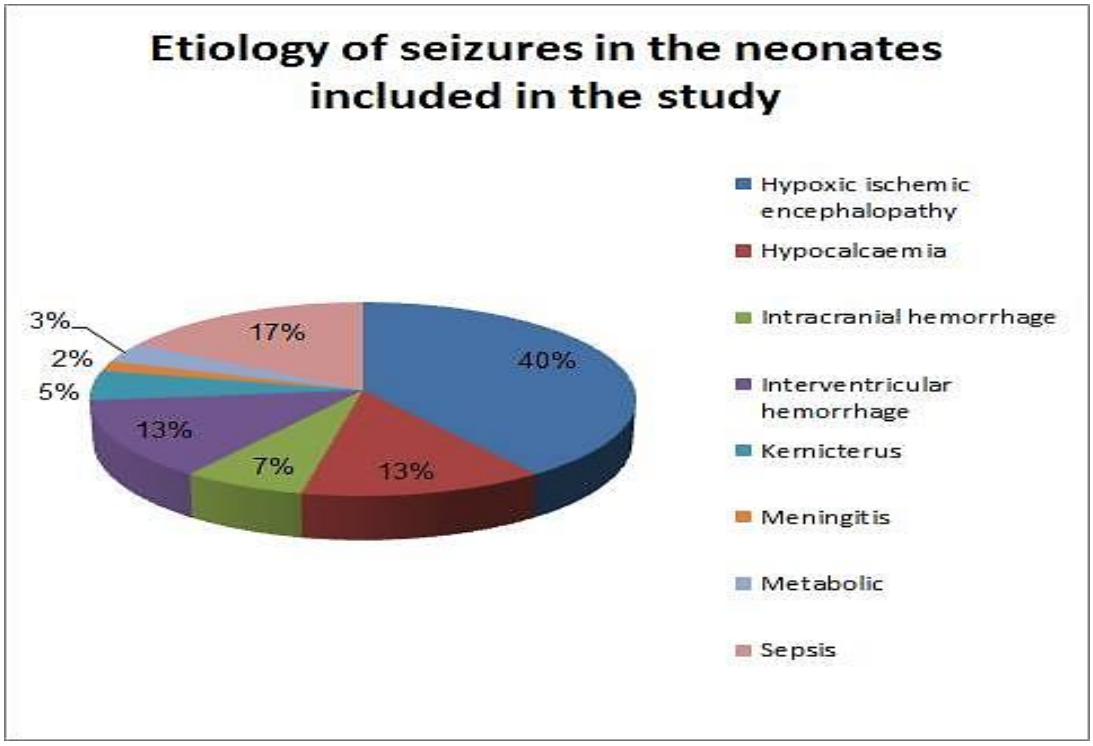

Figure (1): Etiology of seizures in the neonates included in the study

The clinical history, presentation, and results of 24 newborns (or 40% of the total) led to the diagnosis of hypoxic ischemic encephalopathy, which was then categorized into two groups according to the Sarnat and Sarnat clinical staging of HIE: The first group of sixteen infants (stage II HIE) had symptoms such as seizures, hypotonia, bradycardia, hyporeflexia, poor suckling, and Moro reflexes. Group II (stage III HIE) consisted of nine infants with severe hypotonia, low body temperature, lack of suckling and Moro reflexes, sleep apnea, and frequent convulsions. As a result of stage II complications, four neonates did not survive, two have cerebral palsy, and seven have global developmental delay. Stage III neonates died.

Intraventricular hemorrhage, metabolic abnormalities, and meningitis were the leading causes of newborn mortality, accounting for 100% of all cases as shown in figure 2.

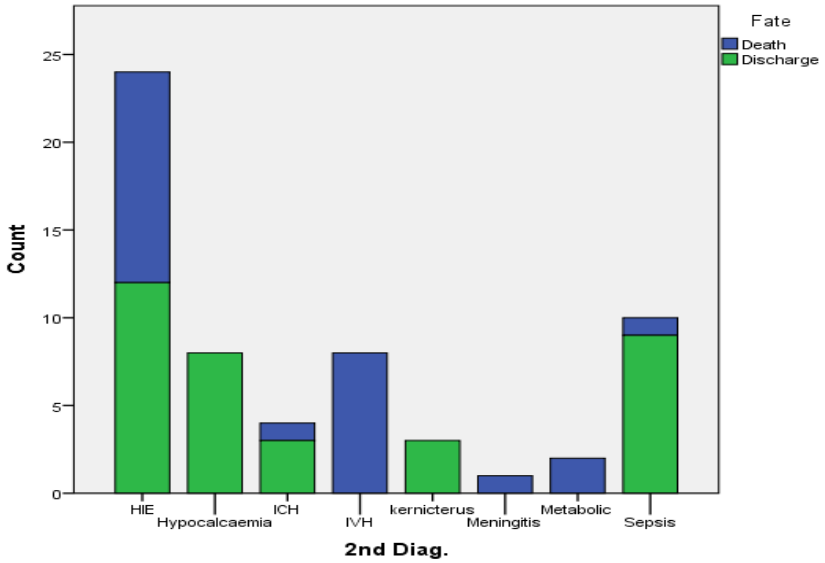

Figure (2): Outcome of 60 NICU cases with neonatal seizures in relation to their etiologies.

In this study, the most prevalent form of seizures observed in neonates was myoclonic seizures, which accounted for 63.3% of all instances on the first day of life and 36.4% of seizures observed between days 2 and week 1, followed by mixed types, which accounted for 47.1% of first-day cases and 52.9% of cases between days 2 and week 1. On the first day of birth, subtle seizures were observed in four cases (or 40% of the total), with similar numbers of clonic and tonic seizures (60%) and one case of subtle type occurring after one week. The relationship between seizure type and onset time was not statistically significant (Table 2).

Table (2): Association between the types of seizures and the times when they began in sixty neonatal intensive care unit cases:

			Age of onset			Total
			D1	D2 – Week 1	> Week 1	
Seizure Type	Myoclonic	Count	14	8	0	22
		%	63.6%	36.4%	0.0%	100.00%
	Mixed	Count	8	9	0	17
		%	47.1%	52.9%	0.0%	100.00%
	Subtle	Count	4	5	1	10
		%	40.0%	50.0%	10.0%	100.00%
	Focal clonic	Count	3	2	0	5
		%	60.0%	40.0%	0.0%	100.00%
	Tonic	Count	3	2	0	5
		%	60.0%	40.0%	0.0%	100.00%
	Multifocal clonic	Count	0	1	0	1
		%	0.0%	100.0%	0.0%	100.00%
Total		Count	32	27	1	60

P-value=0.649

Myoclonic seizures were associated with poor outcome (death in 59.1%) whereas most of cases with mixed and subtle types were discharged in ratios of (70.6%) and (90%) respectively, however all cases with tonic and multifocal clonic seizures died (Figure 3).

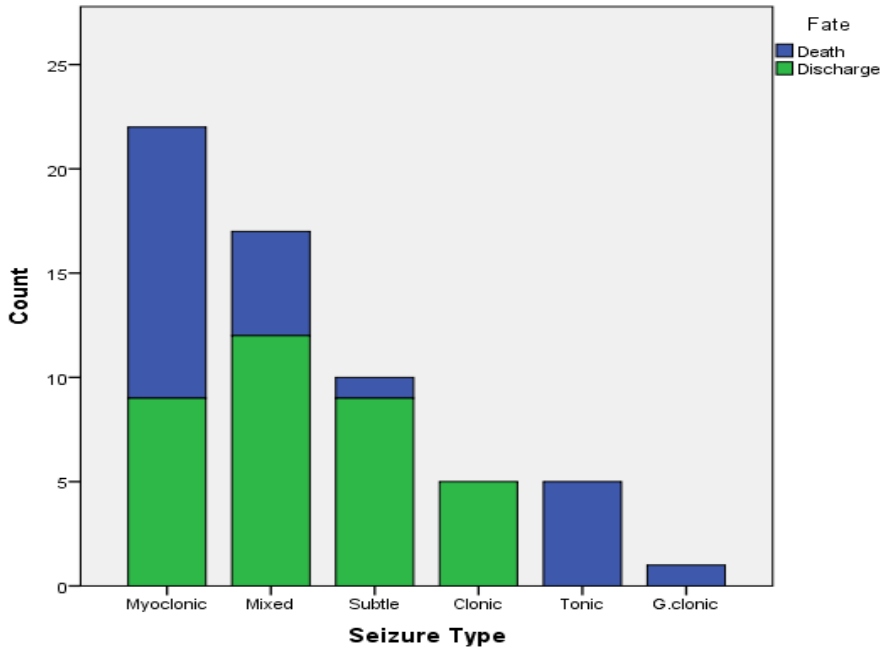

Figure (3): Association between 60 NICU cases' seizure kinds and outcomes

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n this study we used 4 anticonvulsant drugs to control seizures in our cases; some cases (14 neonates) were controlled on monotherapy while the rest (38 neonates) required polytherapy. We observed poor outcome among the polytherapy use of certain anticonvulsant drugs especially levetiracetam, lamotrigine and midazolam (Table 3).

Table (3): Comparison between anticonvulsant treatments of patients included in the study as regard to the outcome:

Treatment		Outcome				P-value
		Death (n=25)		Discharge (n=27)		
		Count	%	Count	%	
Levetiracetam	No	14	34.1%	27	65.9%	<0.001
	Yes	10	100.0%	0	0.0%	
Lamotrigine	No	19	41.3%	27	58.7%	0.009
	Yes	6	100.0%	0	0.0%	
Midazolam	No	1	3.8%	25	96.2%	<0.001
	Yes	24	92.3%	2	7.7%	
Phenytoin	No	1	7.7%	12	92.3%	0.001
	Yes	24	61.5%	15	38.5%	
Phenobarbital	Yes	25	48.1%	27	51.9%	0.001

Cases that required polytherapy antiepileptic drugs (AED) showed poor outcome with death in 92.3%, There was a statistically significant difference for partially controlled seizures (Table 4).

Table (4): Correlation between number of anticonvulsant drugs and outcome:

No of drugs used		Outcome		Total
		Death	Discharge	
Completely controlled (1 drug)	Count	1	13	14
	%	7.1%	92.9%	100.00%
Partially controlled (2 drugs)	Count	0	12	12
	%	0.0%	100.0%	100.00%
Resistance (>2 drugs)	Count	24	2	26
	%	92.3%	7.7%	100.00%

P-value <0.001

Abnormalities on cerebral ultrasonography were significantly associated with clinical examination findings of jaundice and low tone (Table 5).

Table (5): Relation between CUS findings and clinical examination:

Clinical examination	Cranial ultrasound (60 neonates)				P-value
	Normal (20)	%	Abnormal (40)	%	
Poor tone	6	30%	28	70%	0.003
Poor reflexes	14	70%	33	82.5%	0.268
Presence of cyanosis	3	13%	7	17.5%	0.806
Presence of jaundice	10	50%	6	15%	0.004
Poor perfusion	6	30%	15	37.5%	0.566
Tachypnea	9	45%	11	27.5%	0.175
Abnormal temperature	14	70%	19	47.5%	0.099

In this study, on cranial ultrasound, 66.7% neonates had abnormal findings. About 30% of them had cerebral edema, 25% had lateral ventricular dilatation, 22.5% had grade 2 and 3 bleeds and 7.5% had germinal matrix hemorrhage, periventricular hyperechogenicity and leukomalacia in equal ratio. Furthermore, most neonates (88.9%) who had grade 2 and 3 bleeds and (66.7%) who had leukomalacia on cranial ultrasound died (Table 6 and figure 4).

Table (6): Relation between CUS findings and outcome:

CUS findings	No. (60)	%	discharged	%	Died	%
Normal	20	33.3%	20	33.3%	0	0
Abnormal	40	66.7%	15	37.5%	25	62.5%
Germinal matrix Hemorrhage	3	7.5%	2	66.7%	1	33.3%
Other bleeds	9	22.5%	1	11.1%	8	88.9%
Periventricular Hyperechogenicity	3	7.5%	2	66.7%	1	33.3%
Lateral ventricular Dilatation	10	25%	4	40%	6	60%
Leukomalacia	3	7.5%	1	33.3%	2	66.7%
Cerebral edema	12	30%	5	41.7%	7	58.3%

Results from correlating EEG patterns with outcomes reveal that a positive sharp Rolandic waves pattern occurred in 24% of the patients and a burst suppression pattern was found in 48% of the cases that died. Three instances (50%) with a positive sharp Rolandic waves pattern were more likely to have cerebral palsy, while five cases (62.5%) with a multifocal spike pattern were more likely to have global developmental delay (Table 7 and figure 4).

Table (7): Relation between EEG pattern and outcome:

EEG pattern	Normal	Global developmental delay	Cerebral Palsy	Death
Normal	18(85.7%)	0	0	0
Positive sharp Rolandic waves	0	1(12.5%)	3(50%)	6(24%)
Excessive sharp waves activity	0	0	0	0
Periodic low voltage activity	1(4.8%)	2(25%)	0	2(8%)
Multifocal spike pattern	2(9.5%)	5(62.5%)	2(33.3%)	3(12%)
Gross asynchronicity high voltage delta activity	0	0	1(16.7%)	0
Persistent marked voltage suppression	0	0	0	1(4%)
Burst suppression pattern	0	0	0	12(48%)
Isoelectric background pattern	0	0	0	1(4%)

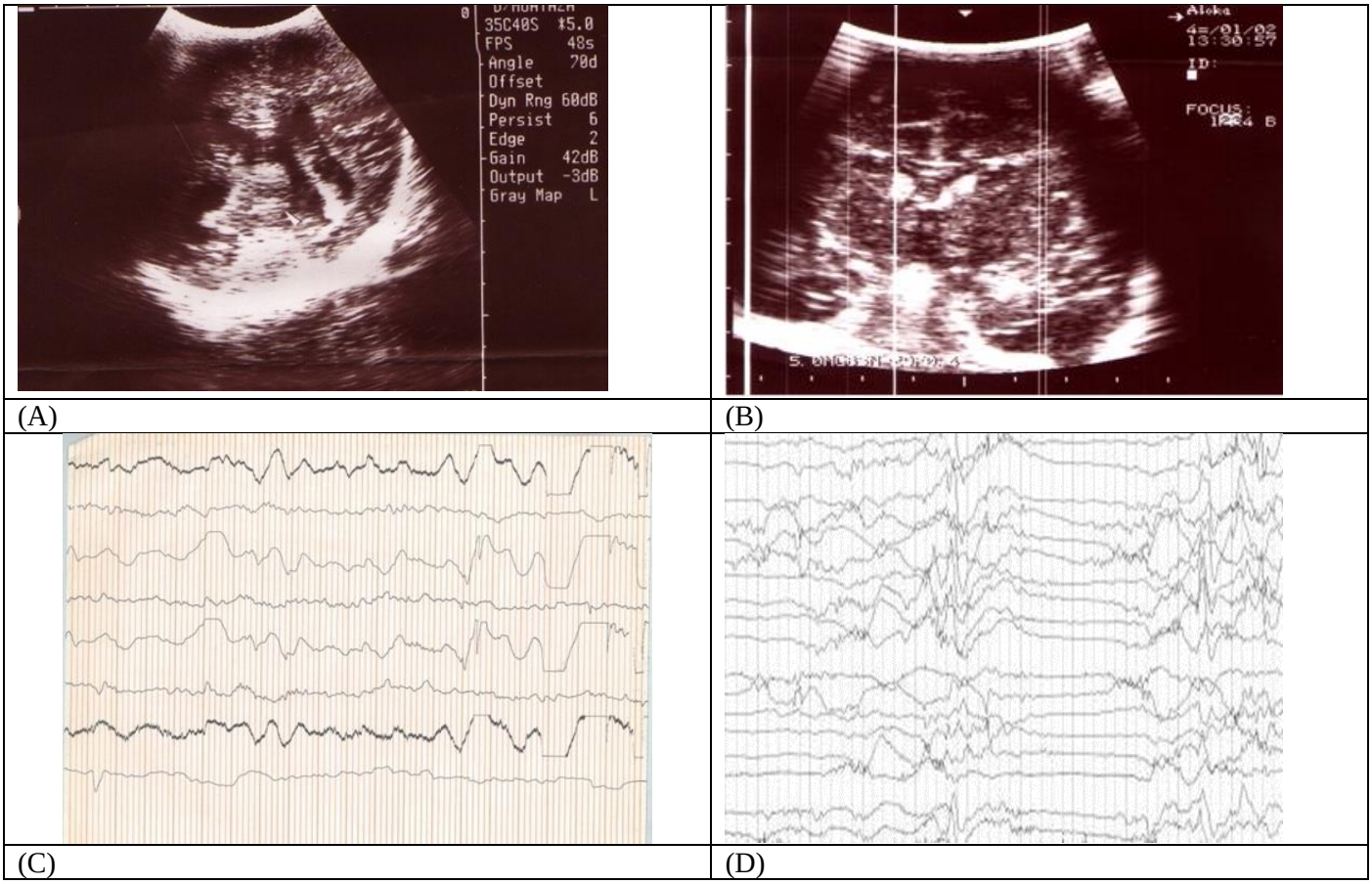

Figure (4): (A): CUS in a coronal plane of 7 day old full term GA=37 weeks, with hypoxic ischemic encephalopathy showing mild dilated lateral ventricles, (B): CUS in a coronal plane of preterm baby GA=33weeks, at the age of 4 days, show bilateral hyperechoic area at the region of the caudate nucleus, indicating germinal matrix hemorrhage (Grade 1), (C): EEG in pre-term baby GA=28 weeks, suffered from hypoxic ischemic encephalopathy on 28 days of life showing spike slow wave complexes, (D): EEG in full-term baby with hypoxic ischemic encephalopathy, showing burst suppression, an alternating pattern of high-voltage mixed frequency activity, and voltage attenuation.

DISCUSSION

Serious neurological diseases often occur alongside seizures in the neonatal era. Because of the neonatal brain's unique neuroanatomical and neurophysiologic development status, convulsive events take on specific, sometimes subtle, shapes [5]. It is simple to identify, diagnose, and treat neonatal seizures. Proper pharmacologic therapies and determining and treating the seizure's underlying cause are essential components of seizure management [6]. It is well-known that video-EEG is the gold standard for detecting seizures in newborns. Nevertheless, not all newborn facilities have access to these equipment [7].

Similarly to the findings in the study by **Das and Debbarma** [8] where term babies made up 91.3% of the total, preterm babies accounted for 7.8%, and postterm babies made up 0.9%, the majority of the neonates with seizures in this study were full-term (60%).

Regarding the impact of gender, our findings indicate a correlation between gender and the frequency of seizures; similarly, **Das and Debbarma** [8] have indicated a higher risk for male newborns. The opposite is true for neonatal seizures; **Talebian *et al.*** [9] discovered that gender had no significant impact.

Within the first twenty-four hours after birth, HIE accounted for forty percent of all newborn seizures in our study. A majority of HIE cases included full-term newborns. Furthermore, this corroborated the findings of **Volpe** [10] who had previously shown that the risk of seizures is comparable in full-term and preterm newborns. Similar findings were published by **Khan *et al.*** [11], who also discovered that the majority of their cases suffered from HIE, and by **Loman *et al.*** [12], who also found that HIE was the earliest common cause of newborn seizures (53.9% in their study). In addition, our findings are in line with those of **Levene** [13], who found that HIE was the cause of seizures in 45.7% of cases within the first 24 hours, which is a greater incidence rate than our own study. Consistent with **Aziz *et al.*** [14], which found a higher frequency of neonatal sepsis at 22% and 19%, respectively, our investigation found that neonatal sepsis was the second most common etiology of neonatal seizures, accounting for 17% of the cases.

Neonatal seizures were shown to be caused by intracranial bleeding in 12 cases (20%) of our study. This includes both intracranial and intraventricular hemorrhage. This was in agreement with **Mizrahi's** [15] findings that intracranial bleeding accounted for 15–25% of the cases of newborn seizures in his study. The incidence of ICH was lower in our study (13% vs. 7.4% vs. 2%), as highlighted by **Aziz *et al.*** [14] **and Kumar *et al.*** [16].

Our study included a wide range of seizure kinds and ratios; for example, 36.7% of the babies had myoclonic seizures, 28.2% had mixed seizures, 16.7% had mild seizures, 5% had both clonic and tonic types, and 1.7% had multifocal clonic fit. **Faiz *et al.*** [17] found similar results while studying 101 infants; 20 (19.8%) had modest seizures, 1 (0.9% of the neonates) had myoclonic fits, and 40 (39.6% of the babies) had both tonic and clonic fits.

The majority of the newborns with seizures in our study (70.8%) were diagnosed with hypoxic ischemic encephalopathy, and 32 (53.3% of the total) of the 60 neonates with seizures began experiencing them on the first day of life. 27(45%) neonates developed sepsis between days 2 and 1 week, while just 1 (1.6%) newborn developed sepsis after one week. This matched the findings of **Holden and Freeman** [18], who found that sepsis caused convulsions in 36 infants (13% of the total) after 7 days. In a study conducted by **Sarkar and Barks** [19], it was shown that seizures started within the first 24 hours of life in 58 cases (44.6%). Seizures began in 66 (or 57.4%) of the 115 neonates in the study by **Das and Debbarma** [8] on the first day of life, and in 24.4% of the cases during the first week.

Out of 52 instances that were first treated with phenobarbital, 14 responded to phenobarbitone alone; 12 were controlled with the addition of phenytoin; and 10 required the addition of midazolam, according to our study. Alternatively, lamotrigine and tiracetam required further control in 16 cases. According to **Rennie and Boylan** [20], phenobarbital should be used as the initial line of treatment for seizures, and if they do not go away, other medications such as diazepam, lorazepam, phenytoin, and midazolam can be added. These results are consistent with their study.

Twelve patients (or 50%) died of hypoxic ischemic encephalopathy, and eight cases (or 100%) died of intraventricular hemorrhage; the overall death rate was twenty-five cases (41.7%) out of sixty. While some studies have found lower rates of mortality from HIE, our results are higher and comparable with those of **Patil *et al.*** [21] (11.25% and 9%, respectively) and **Tekgul *et al.*** [22] (7%). The cause of the seizures may account for this increased frequency. The results of cerebral ultrasonography were abnormal in 66.7% of the newborns. Brain edema affected over 30%, intracranial hemorrhage about 29.5%, and ventriculomegaly and periventricular hemorrhage about 25% of patients. An equal proportion of cases of hyperechogenicity and leukomalacia were observed (7 percent).

CONCLUSION

While the prognosis is dismal for seizures that have persisted for a long period, it improves when neonatal seizures are controlled early on. It is possible to detect mild to moderate brain lesions using a combination of neuro-imaging and newborn EEG.

Conflict of interest: none declared.

Fund: non-fundable.

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