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Retrospective Evaluation of Etiological and Prognostic Factors of Neonatal Convulsions

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Abstract

Objective: Seizures observed in newborns are a common, challenging to diagnose and treat, high-mortality-rate condition that is associated with a risk of long-term neurodevelopmental disorders. We aimed to determine the causes, characteristics, and prognosis of neonatal seizures.

Methods: In this retrospective study, a total of 41 cases with a diagnosis of neonatal convulsion were evaluated at the Neonatology Unit of Pamukkale University School of Medicine between January 2015 and 2023.

Results: Of the newborns experiencing seizures, 56% were male, and 63.4% were female. Among the cases, 63.4% were born at term, 26.8% were born at 34-37 weeks gestation, and 9.7% were born before 34 weeks gestation. The most common seizure type observed was multifocal clonic seizures (36.5%). The main diagnoses in newborns experiencing seizures were hypoxic–ischemic encephalopathy (HIE) (31.7%) and metabolic disorders (14.6%). The mortality rate during the average follow-up of 35 ± 9.8 months was 9.7%. Low Apgar score and epilepsy were associated with adverse neurodevelopmental outcomes.

Conclusion: Since HIE and hypoglycemia are the most common causes of neonatal seizures, efforts should be made to improve care during birth and early breastfeeding period.

Keywords: Neonate, convulsion, etiology

Introduction

Neonatal seizures (NSs) are the most common neurological disorder in newborns and often serve as an initial sign of neurological dysfunction.[1] They are associated with a high rate of morbidity and mortality.[2] Although a single, nonrecurrent NS can have a good prognosis, approximately 30% of surviving infants may develop neurodevelopmental disorders or epilepsy later in life. Studies have shown that the mortality rates of NSs range from 2.4% to 17%.[2-4] The etiology of NS is highly heterogeneous and often acute symptomatic. Identifying the underlying causes of NS is crucial, as it has a significant impact on prognosis, outcomes, and influences advanced treatment strategies.[5,6] Hypoxic–ischemic brain injury, hypoglycemia, preterm birth, and fetal distress are among the most common causes of NSs.[7] Therefore, investigating the underlying causes and factors associated with mortality in NSs appears necessary. Other risk factors for NSs include postnatally diagnosed maternal hypothyroidism, 5-minute Apgar scores, intracranial thrombosis, metabolic disorders, and intracranial infections.[8,9] Genetic factors also play a role in the incidence of NSs, as studies have identified responsible mutations in familial NSs.[10] Diagnosing seizures can be challenging as they can be uncertain or subclinical and may only be observed in electrographic recordings.[11] Electroencephalography (EEG) or amplitude-integrated EEG (aEEG) is necessary for accurate diagnosis.[12,13] The etiology of NSs is highly heterogeneous and often acute symptomatic. Identifying the underlying causes is crucial, as it significantly impacts prognosis, outcomes, and influences advanced treatment strategies.[5] Neonatal seizures are mostly focal, but generalized seizures have also been described in rare cases, and their clinical presentations vary widely. Evaluating the combination of etiological factors, clinical presentation, different diagnostic tools, and treatments, as well as neurodevelopmental outcomes, can broaden physicians' perspective on NSs. In our study, we aimed to determine the causes, characteristics, and prognosis of NSs.

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Methods

In this descriptive cross-sectional retrospective study, a total of 41 cases, including term and preterm infants, diagnosed with neonatal convulsion and followed up and treated at the Neonatal Intensive Care Unit of Pamukkale University School of Medicine Hospital between January 2015 and 2023, were included. Newborns who did not attend outpatient clinic visits were excluded from the study. The study obtained ethical approval from the Pamukkale University School of Medicine Ethics Committee on February 7, 2023 (Approval No: 03).

Gender (male/female), gestational age (GA) (<34 weeks, 34-37 weeks, and >37 weeks), birth weight (BW), mode of delivery (cesarean section and vaginal delivery), 5-minute Apgar score, cerebrospinal fluid results for patients who underwent lumbar puncture, admission and duration in the unit, need for mechanical ventilation, family history of epilepsy, neuro/physical developmental status, time of seizure occurrence (within the first 24 hours, 24-72 hours, and after 72 hours), seizure type (tonic, clonic, myoclonic, and subtle), imaging methods (transfontanelle ultrasonography, magnetic resonance imaging (MRI), and computed tomography) were evaluated. The causes of seizures (hypoxic–ischemic encephalopathy (HIE), infection, brain developmental anomaly, cerebral infarction, hemorrhage, maternal drug withdrawal, genetic, hyperbilirubinemia, unknown), use of antiepileptic drugs at discharge, and type of anticonvulsant used in treatment (levetiracetam, phenobarbital, topiramate, and phenytoin) were assessed. Hypoxic–ischemic encephalopathy was defined according to the guidelines of the American College of Obstetricians and Gynecologists.[14] Birth weight was categorized as normal: 2500-4000 g, low BW (LBW): 1500-2499 g, and very low BW < 1500 g. The EEGs were performed between the first day and the 22nd day of admission in the cases, with the earliest EEG taken on the day of admission. The EEGs of patients diagnosed with HIE were obtained during admission. All EEGs were interpreted by a pediatric neurologist as normal, mildly abnormal, or moderately to severely abnormal.[15]

Statistical Analysis

Descriptive analysis was used to present the results, including mean ± standard deviation for quantitative variables and frequency (percentage) for categorical variables. The relationship between variables was tested using Fisher's exact test. For statistical analysis, Statistical Package for the Social Sciences Statistics (SPSS) software, version 18.0 for Windows (SPSS Inc., Chicago, Ill, USA) was used. *P*-values of .05 or lower were considered statistically significant.

Results

In this descriptive cross-sectional retrospective study, a total of 41 cases of term and preterm newborns diagnosed with NSs and followed up and treated at the Neonatal Intensive Care Unit of Pamukkale University Faculty of Medicine Hospital between January 2015 and 2023 were included. Newborns who did not come for outpatient follow-up were excluded from the study. The study was approved by the Ethics Committee of Pamukkale University Faculty of Medicine on February 7, 2023, with approval number 03. The gender distribution was 56% male and 44% female. The mean follow-up duration was 35 ± 9.8 (range: 3-38) months. Among the cases, 63.4% were born at term, 26.8% were born at 34-37 weeks of gestation, and 9.7% were born before 34 weeks of gestation. The mean GA was 36.99 ± 1.33. Based on BW, 80.4% were appropriate for GA, 9.7% were large for GA, and 9.7% were small for GA. The mean BW was 2.45 ± 1.74 grams. Regarding the mode of delivery, 73.1% were delivered by cesarean section, and 26.8% were delivered by normal vaginal delivery. A family history of epilepsy was present in 12.1% of the cases. The fifth minute Apgar score was 8 ± 1 .24. The mean length of hospital stay for all newborns was 40.1 ± 33 days, and 41% of them required mechanical ventilation (Table 1). Among the seizure types, the most common was multifocal clonic seizures (36.5%), followed by focal tonic seizures (14.6%), focal clonic seizures (19.5%), subtle seizures (12.1%), and myoclonic seizures (17.1%) (Figure 1). The onset of seizures occurred within the first 24 hours of life in 34.1% of newborns. The EEG results showed that 76% had normal to mildly abnormal EEG findings, while 24% had moderate to severely abnormal findings. Lumbar puncture (LP) results revealed abnormal findings (pleocytosis, high protein, and low sugar) in 24.3% of cases, and brain tomography was performed in 9 patients, with pathology detected in 4 of them. Magnetic resonance imaging was performed in 26 patients, with abnormalities observed in 15 cases. Transfontanelle ultrasonography was performed in 31 patients, and abnormalities were found in 15 cases. Among the cases with abnormal imaging findings, 69.6% were suggestive of vascular processes (ischemia and stroke), 14.6% had structural brain anomalies, and 15.8% were classified as unspecified findings. The most common diagnosis among newborns with seizures was HIE (31.7%), followed by metabolic causes. Among the metabolic causes, 4 patients had hypoglycemia, 1 patient had hypocalcemia, and 1 patient had congenital metabolic disease nonketotic hyperglycinemia (Figure 2). The main antiepileptic drugs used to control seizures included phenobarbital (66.1%) and levetiracetam (45.2%), while the frequency of other drugs

Table 1. The Association of Demographic Characteristics

Variables	n (%)
Sex (male/female) n (%)	23 (56)/18 (44)
Gestational age (weeks), n (%)	
<34	4 (9.7)
34-37	4(9.7)
>37	33 (80.1)
Type of delivery (C/S/NVD) (%)	73.1/26.8
Neonatal deaths, n (%)	4 (9.75)
Family history of epilepsy, n (%)	5 (12.1)
Ventilation need, n (%)	16 (41)
Convulsion time (hours), n (%)	
<24	15 (34.1)
24-72	13 (33)
>72	13 (32.9)
EEG, n (%)	
Normal	15 (36)
Slightly abnormal	16 (40)
Moderately abnormal	10 (24)
Seizure at discharge	8 (20)
Type of AED used, n (%)	
Phenobarbital	27 (66.1)
Levetiracetam	20 (48.5)
Topiramate	3 (5.6)
Phenytoin	2 (3.2)

AED, Antiepileptic drug; C/S, cesarean; EEG, electroencephalogram; NVD, normal vaginal delivery.

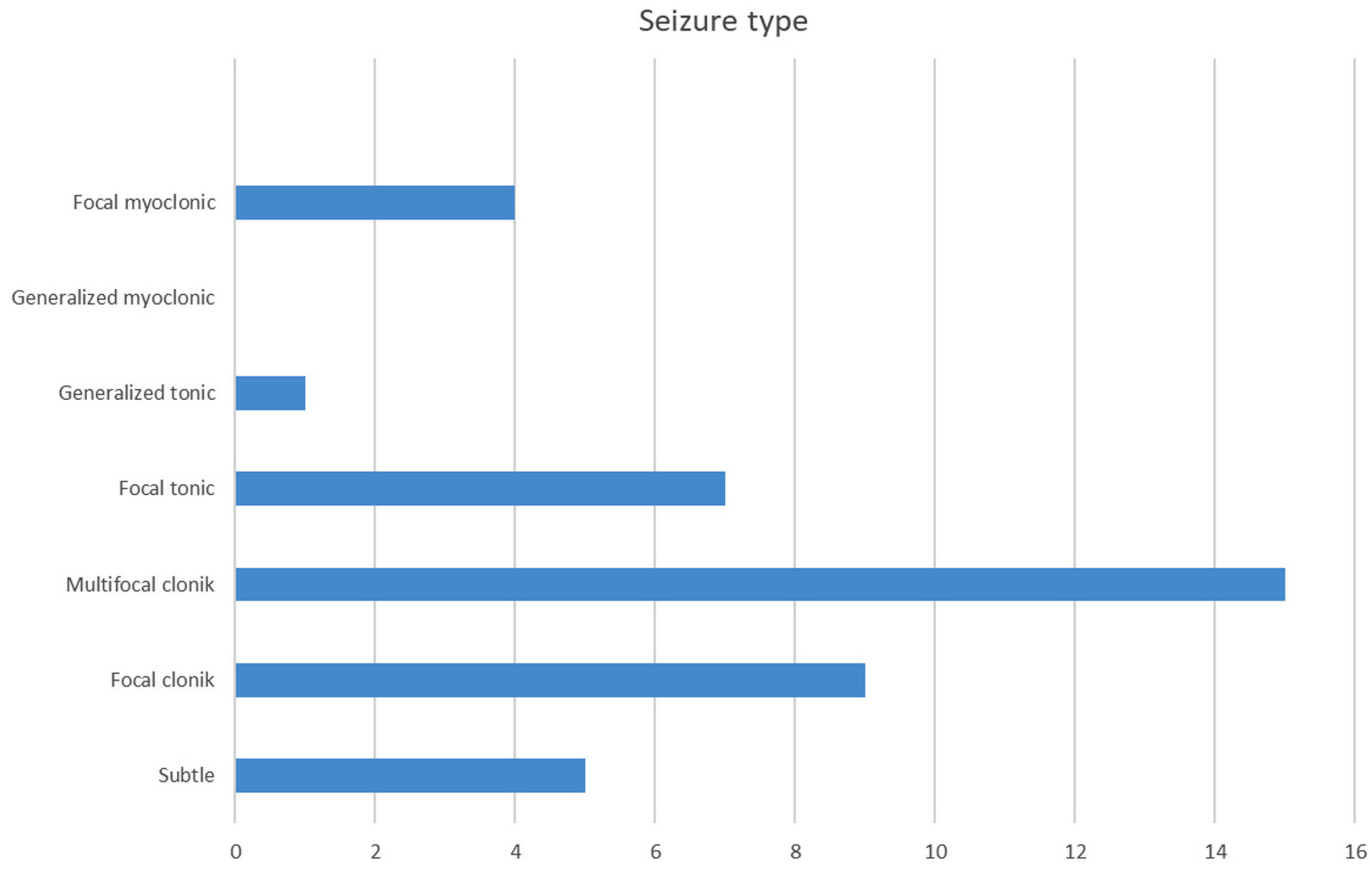

Figure 1. Types of epilepsy.

was less than 10%, with 48.5% using monotherapy, and 31.4% using combination therapy.

Discussion

The results of this study showed that NSs are more commonly observed in males, normal weight, and term infants. During an average follow-up period of 35 ± 9.8 months, a mortality rate of 9.75% was identified. Ronen et al's[2] study found a 30% higher mortality rate in preterm infants compared to full-term infants, which is consistent with other studies reporting mortality rates between 11% and 13%. Most studies have identified HIE as the most common etiology, as observed in our study.[3,16-18] These findings highlight the need for increased attention to neonatal and maternal care, as HIE treatment is challenging and associated with unfavorable outcomes.[18] Neonatal epilepsy is usually an early manifestation of postneonatal epilepsy. The etiology of NSs is heterogeneous and often associated with hypoxic–ischemic events, stroke, or infections in term infants, although sometimes it remains unknown. In preterm infants, intraventricular hemorrhage is the most common cause of seizures.[19,20] In our study, we observed an infection frequency of 14.6%. Studies conducted in developed countries have reported seizure frequencies related to infection between 4% and 20%,[2,21,22] whereas studies in developing countries have reported rates between 8% and 60%.[23-25] Lai et al[26] reported an approximate frequency of 8% in Taiwan, while a study conducted in Iran also reported a similar frequency.[24] Generally, these high rates may be attributed to families not wanting to undergo LP. Consistent with previous studies, our study identified the most common time for seizures to occur as within the first 24 hours.[3,27] The timing of NSs can vary depending on the etiology, with the highest occurrence within the first week and 25%-55% of cases manifesting within the first 24 hours.[28] Particularly in infants diagnosed with HIE, seizures often appear within the first 24 hours. The most frequently observed seizure type in our study was clonic seizures, accounting for 56% of cases. There are varying opinions regarding the most common seizure type during the neonatal period. Similarly, Tekgül et al[18] reported clonic seizures as the most common type, with a prevalence of 61%. In contrast, Volpe[29] reported a prevalence of 54% for subtle seizures, while Cornell[30] indicated a prevalence of 39% for subtle seizures as the most common type. The differences in these findings may be attributed to demographic and epidemiological variations among different studies or variations in the

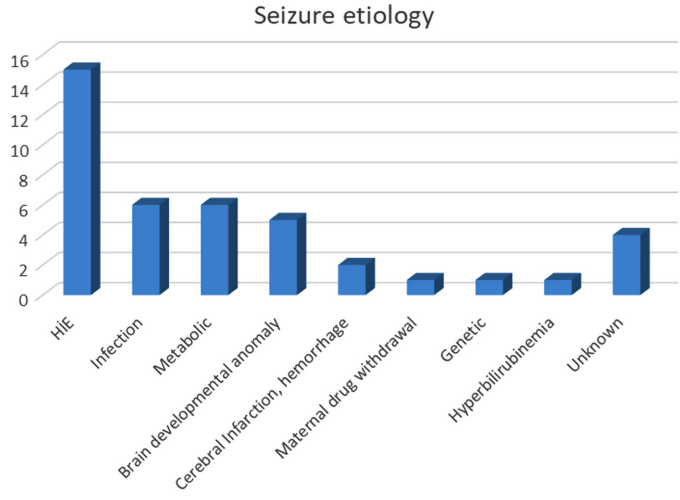

Figure 2. Seizure etiology.

accuracy of diagnostic tools used. Santaron et al [31] emphasized that focal clonic seizures are associated with acute symptomatic seizures, while focal tonic seizures are related to neonatal epilepsy. Luying Li et al [32] linked 50% of tonic seizures and a single consecutive seizure case (tonic followed by automatisms) to genetic factors, and they found that clonic seizures were relatively more common in acute symptomatic seizures. When considering long-term outcomes, factors such as Apgar score, abnormal neurological examination, abnormal background activity on EEG, status epilepticus, and the presence of brain injury on imaging (involving deep gray matter or brainstem) have negative effects.[33] In our study, adverse neurodevelopmental outcomes occurred in 36% of patients, and this was significantly associated with abnormal neurological examination ($P = .006$), low 5-minute Apgar score ($P = .002$), epilepsy ($P < .001$), and abnormal imaging findings ($P < .001$). Therefore, health-care professionals, including doctors and nurses, need to pay sufficient attention to risk factors for neurodevelopmental delay and educate mothers on this matter to reduce morbidity rates.[34,35] However, the outcomes of the most appropriate drug regimen appear to be controversial.[4] Learning difficulties, spasticity, and epilepsy are the main neurological sequelae in patients with neurodevelopmental impairments and have been reported in various studies between 28% and 60% of cases.[21,36] Among our cases, sequelae were observed in 25% of those experiencing tonic seizures, 34.7% of those experiencing clonic seizures, 40% of those experiencing subtle seizures, and 50% of those experiencing myoclonic seizures.Gürbüz et al[37] found a higher rate of sequelae in cases of clonic seizures. Pisani's[34] study in 2009 also concluded that myoclonic seizures were associated with a poor prognosis. In addition, Tekgül et al,[18] in their study of 89 patients, reported that 7 patients had myoclonic seizures, and none of them had any sequelae. The variation in patient numbers and the inclusion of some preterm and term infants together in these studies have led to different results.

The significant relationship between abnormal imaging findings and 1-minute Apgar score with neurodevelopmental delay in long-term follow-ups necessitates greater attention to maternal/neonatal care and the collection of detailed histories during childbirth.

Limitations

This study has several limitations. First, its retrospective nature has an inherent weakness in evaluating the appropriateness of current practices in managing NS, including limited video EEG monitoring duration and clinical follow-up. Second, not all patients underwent MRI. Third, the low number of cases may affect the statistical significance of the results. Fourth, the EEG and seizure classification for the patients are not up-to-date since our patients were gathered from 2015 onwards. Further studies are needed to analyze specific epileptic subtypes among a larger patient cohort.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Pamukkale University (Approval no: 03, E-60116787-020-336004, Date: February 7, 2023).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Study Concept/Design – O.G.; Data Collection – M.T., O.G.; Data Analysis/Interpretation – Ö.Ö., EK., M.T.; Manuscript Drafting – O.G., M.T., B.Y.; Critical Review of Content – O.G., Ö.Ö.; Final Approval and Responsibility – O.G., M.T.; Material and Technical Support – M.A.; Supervision – O.G., E.K.

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