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Evaluation of Etiological Causes and Demographic Characteristics of Neonatal Seizure in Adiyaman University Training And Research Hospital, Türkiye: A Retrospective Study

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Abstract

Aim: Neonatal seizures are different from seizures seen at other ages in terms of etiology, clinical follow-up, treatment and prognosis. The purpose of this study was to determine the etiological causes and demographic characteristics of neonates admitted due to seizures in the neonatal intensive care unit.

Methods: This is an original study involving newborns hospitalized for seizures in the neonatal intensive care unit at Adıyaman University Training and Research Hospital. The files of 40 patients followed up due to seizures between September 2016 and July 2021, were examined retrospectively. 40 out of 45 patients satisfied the inclusion criteria. The files of 40 patients were retrospectively analyzed in terms of age, sex, gestational age, birth weight, mode of delivery, APGAR score, seizure etiology, intervention and treatment, electroencephalography (EEG), trans fontanel ultrasonography (USG) and brain magnetic resonance imaging (MRI) findings, length of hospital stay, and mortality rates.

Results: The study group consisted of 40 patients, 21 girls (52.5%) and 19 boys (47.5%). Twenty-seven (67%) of the patient group were born at term and 13 (33%) preterm. The mean birth week was 38, and the mean birth weight was 2900 g. The underlying seizure etiology was unknown in 37.5% (n = 15) of cases, while the most common known etiological cause was hypoxic ischemic encephalopathy, seen in 20% (n = 8). The mortality rate in our patient group was 22.5% (n = 9).

Conclusion: Among the known causes of neonatal convulsions, hypoxic-ischemic encephalopathy in term babies and germinal matrix bleeding in preterm babies were found to be the most common causes. However, despite all kinds of examinations and evaluations, the cause of a significant portion of them has not been determined. Long-term follow-up of newborns with convulsions is required to detect early neurodevelopmental problems that may develop during follow-up.

Key words: Etiology, neonatal, seizures

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Türkiyede Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesinde Yenidoğan Nöbetlerinin Etiyolojik Nedenleri ve Demografik Özelliklerinin Değerlendirilmesi: Retrospektif Bir Çalışma

Öz

Amaç: Yenidoğan nöbetleri etiyoloji, klinik takip, tedavi ve prognoz açısından diğer yaşlarda görülen nöbetlerden farklıdır. Bu çalışmanın amacı, yenidoğan yoğun bakım ünitesinde nöbet nedeniyle yatırılan yenidoğanların etiyolojik nedenlerini ve demografik özelliklerini belirlemektir.

Yöntemler: Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi Yenidoğan Yoğun Bakım Ünitesinde nöbet nedeniyle yatırılan yenidoğanları kapsayan özgün bir çalışmadır. Eylül 2016 ile Temmuz 2021 tarihleri arasında nöbet nedeniyle takip edilen 40 hastanın dosyaları retrospektif olarak incelendi. 45 hastanın 40'ı dahil etme kriterlerini karşıladı. 40 hastanın dosyası yaş, cinsiyet, gebelik yaşı, doğum ağırlığı, doğum şekli, APGAR skoru, nöbet etiyolojisi, müdahale ve tedavi, elektroensefalografi (EEG), transfontanel ultrasonografi (USG) ve beyin manyetik rezonans görüntüleme (MRG) bulguları, hastanede kalış süresi ve ölüm oranları açısından retrospektif olarak analiz edildi.

Bulgular: Çalışma grubu 21 kız (%52,5) ve 19 erkek (%47,5) olmak üzere toplam 40 hastadan oluşmaktadır. Hasta grubunun 27'si (%67) term, 13'ü (%33) ise preterm doğmuştu. Ortalama doğum haftası 38 ve ortalama doğum ağırlığı 2900 g idi. Olguların %37,5'inde (n = 15) altta yatan nöbet etiyolojisi bilinmezken, bilinen en yaygın etiyolojik neden %20'sinde (n = 8) görülen hipoksik iskemik ensefalopatiydi. Hasta grubumuzda mortalite oranı %22,5 (n = 9) idi.

Sonuç: Yenidoğan konvülsiyonlarının bilinen nedenleri arasında term bebeklerde hipoksik-iskemik ensefalopati ve preterm bebeklerde germinal matriks kanaması en sık nedenler olarak bulunmuştur. Ancak her türlü inceleme ve değerlendirmeye rağmen bunların önemli bir kısmının nedeni belirlenememiştir. Konvülsiyon geçiren yenidoğanların uzun süreli takibi, takip sırasında gelişebilecek erken nörogelişimsel sorunların saptanması için gereklidir.

Anahtar kelimeler: Etiyoloji, yenidoğan, nöbet.

INTRODUCTION

One of the most common disorders in newborn infants is seizure activity[1]. They represent transient changes that occur with abnormal, sudden overstimulation of groups of neurons. Neonatal seizures may indicate underlying brain damage[2]. The fact that neonates possess immature neurons and neurotransmitter level differences makes them more susceptible to seizures. These may be observed in 3.5 infants out of every 1000 live births[3]. Several etiological causes might induce them. Birth weight, gestational age, APGAR score, intervention requirement in the delivery room, EEG, brain MRI and trans fontanel USG results are also important predictors of prognosis. Additionally, preterm newborns' etiological status is different from that of term babies[4]. Treatment depends on the etiology. Early and appropriate intervention improves prognosis by preventing further brain damage. Therefore, it is important to determine the cause of seizures in newborns to determine prognosis and initiate appropriate treatment.

Hypoxic ischemic encephalopathy in term babies and germinal matrix bleeding in premature babies are the leading causes of convulsions in newborns. In addition, congenital metabolic diseases, infections, metabolic disorders, central nervous system malformations, and B6-dependent seizures are important causes of convulsions detected in newborns.

The purpose of this study was to determine the etiological causes and demographic characteristics of neonates admitted due to seizures in the neonatal intensive care unit.

METHODS

Type of the study

This is an original study involving newborns hospitalized for seizures in the neonatal intensive care unit at Adıyaman University

Training and Research Hospital between September 2016 and July 2021.

Population and sample of the study

Non-epileptic paroxysmal events were excluded. 40 out of 45 patients satisfied the inclusion criteria. The files of 40 patients were retrospectively analyzed in terms of age, sex, gestational age, birth weight, mode of delivery, APGAR score, seizure etiology, intervention and treatment, EEG, transfontanelle USG and brain MRI findings, length of hospital stay, and mortality rates.

Data collection tools

"Turkish Neonatal Society Guideline on Neonatal Encephalopathy" was used for the diagnosis of hypoxic-ischemic encephalopathy [5]: accompanying acute peripartum/intrapartum event 1) Apgar score <5 at the 5th and 10th minutes, 2) pH <7 and BE< -12 mmol/L in fetal umbilical blood gas, 3) Presence of clinical findings (hypotonic, hypoactive, lack of sucking, absence of Moro reflex, convulsion). Metabolic disease screening was planned by performing the necessary tests for the suspected disease in the newborn with symptoms. (Tandem mass, blood amino acids, organic acid in the urine, reducing substance in stool, specific enzyme analysis). The diagnosis of convulsion was made clinically. The decision was made by the neonatologists after the abnormal movement observed in the newborn. While cranial ultrasonography was performed on all patients, EEG and brain MRI were performed on some of them.

Analysis of data

The results of the patients were also statistically evaluated using the statistical package program SPSS for Windows (ver. 20.0, IL, USA). The conformity of the measurement values to the normal distribution was examined graphically and using the Shapiro-Wilk test. The number and frequency rates of the data were specified. Mean ± standard deviation was used for descriptive statistics of normally distributed measurements while the median was used for the descriptive statistics of measurements that do not show normal distribution.

Ethics committee approval

All procedures were by the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval for the study was obtained from the ethics committee of the hospital (No: 2022/3-30).

RESULTS

The medical records of 45 patients who were followed up in the neonatal intensive care unit of Adıyaman University Training and Research Hospital between September 2016 and July 2021 with a history of seizures were reviewed retrospectively. The five patients having a history of non-epileptic paroxysmal events and insufficient file data were excluded from the study. Forty patients meeting the inclusion criteria were thus included in the study. The study group consisted of 40 patients, 21 (52.5%) girls and 19 (47.5%) boys. The female/male ratio was 1.1. The median gestational age of the patient group was about 38 (min-max of 24 - 41), with a median birth weight of 2900 g (min-max of 800 - 4150 g). 27 of the patients (67%) were born at term while 13 (33%) were preterm. 13% of our patients had birth weights lower than 2500 g.

The median APGAR scores of patients at 1 minute and 5 minutes were respectively five (min-max of 2 - 8) and six (min-max of 3-9). The 45% (n = 18) of the patients received postnatal resuscitation. The 14 (35%) patients were born by cesarean section (C/S) while 26 (65%) were by normal spontaneous vaginal delivery (NSVD) (Table 1).

Table I: Demographic and perinatal characteristics of the patients (n= 40)

Parameter		Frequency (Percentage)
Gender		
Female	n (%)	21 (52.5%)
Male	n (%)	19 (47.5%)
Birth		
week	Median (min-max)	38 (24-41)
weight (g)		2900 (800-4150)
Mode of delivery		
Cesarean section	n (%)	14 (35%)
Normal spontaneous vaginal delivery	n (%)	26 (65%)
Birth time		
Term	n (%)	27 (67%)
Preterm	n (%)	13 (33%)
APGAR score		
1st min	Median (min-max)	5 (2-8)
5th min		6 (3-9)
Apgar score less than 7 at 5th minute	n (%)	17 (42.5%)
The need for resuscitation in the delivery room	n (%)	18 (4 %)
Birth weight under 2500 g	n (%)	13 (33%)

Etiological causes in the neonatal period were unknown in 37.5% (n = 15) of cases, while the most common known cause was hypoxic ischemic encephalopathy (HIE) at a rate of 20% (n = 8), Table 2.

Table II: Etiology of seizures in the patients

Parameter		Frequency (Percentage)
Hypoxic ischemic encephalopathy	n (%)	8 (20%)
Intracranial hemorrhage		5 (12.5%)
Hypocalcemia		5 (12.5%)
Hypoglycemia		4 (10%)
Hydrocephalus		1 (2.5%)
Metabolic Disease		1 (2.5%)
Cerebral Dysgenesis		1 (2.5%)
Idiopathic		15 (37.5%)

Phenobarbital was the most frequently employed antiseizure drug, used by 22 (55%) patients, while six (15%) used dual antiseizure drugs. It was observed that 35% (n = 14) of the patients used antiseizure drugs at discharge. In our patient group, eight (20%) patients had pathological transfontanel USG results, and nine (22.5%) patients had pathological brain MRI results. Abnormal results were also observed in four (10%) of the 12 patients who underwent EEG, (Table 3).

Table III: Clinical and laboratory findings and treatment and prognosis in the patients

Parameter		Frequency (Percentage)
Only phenobarbital treatment was started	n (%)	22 (55 %)
Two antiseizure treatments were started		6 (15 %)
Number of patients responding to pyridoxine treatment, n (%)		2 (5 %)
With pathological cranial ultrasonography findings		8 (20 %)
With pathological cranial magnetic resonance findings		9 (22.5 %)
Patients with pathological findings at discharge		8 (20 %)
Number of patients using antiseizure at discharge		14 (35 %)
EEG not taken		28 (70 %)
With abnormal EEG findings		4 (10 %)
Mortality		9 (22.5 %)
Length of hospital stay (days)	Median (min-max)	17.5 (3-190)

Pathological magnetic resonance findings were as "signal increase in basal ganglia, cystic encephalomalacia, an increased signal in periventricular white matter, subcortical tissue loss, cerebral atrophy, dilation of the ventricles, bleeding-ischemia-stroke." Pathological cranial ultrasound findings were "increased echogenicity in the basal ganglia, brain edema, fainting in the ventricles, bleeding-ischemia-stroke, dilation of the ventricles, hydrocephalus, periventricular cystic encephalomalacia."

DISCUSSION

Children are generally at the greatest risk of seizure in the postnatal first month[6]. Neonatal seizures are the most frequent neurological symptom in the postnatal period and are more common in boys than girls. However, although the female gender predominated, the female/male ratio was just about 1.1 in the present study. It is known that gestational age and birth weight have more effects on morbidity and mortality in newborns. Especially preterm babies are more affected than term babies.

Although vaginal delivery (VD) is usually described as the best form of delivery, the VD rate is decreasing due to increasing rates of cesarean section (C/S). However, it was observed that the majority of our patients had a history of birth with VD. An APGAR score lower than seven at 5 min is one of the criteria for perinatal asphyxia. A score lower than three indicates severe, and a score lower than seven shows moderate neuro/cardiorespiratory depression[7]. The median APGAR score at 5 min among our patients was six and our lowest APGAR score was three.

Seizures emerging in the neonatal period may be the first and only clue regarding an underlying neurological pathology. The most frequent reason for neonatal seizures remains to be HIE[8]. Other reasons include intracranial hemorrhage, perinatal stroke, metabolic and electrolyte disorders, systemic and central nervous system infections, congenital metabolic diseases, and genetic epilepsy syndromes[9]. Nair et al. identified HIE as the most common cause, and hypocalcemia as the most common metabolic cause[10]. In agreement with the previous studies, HIE was also the most common cause, and hypocalcemia was the most frequent metabolic cause in our study group. In the study reported by Ekici et al., they stated that the two most common causes of convulsions in babies during the neonatal period were hypoxic-ischemic encephalopathy (31.2%) and hypoglycemia (8.2%)[11]. In 37.5% of our patient group, however, the underlying cause could not be determined.

History and physical examination completed with video EEG/aEEG (amplitude integrated) and cerebral imaging techniques can assist with the early identification of underlying etiologies which is important for follow-up and prognosis[12]. EEG is regarded as the gold standard for the diagnosis of seizures in newborns. However, it is not available on a 24/7 basis in many neonatal units due to the need for time allocation, costly equipment, and specialist interpretation[13]. EEG was performed on only 30% of our patient group, with abnormal results being observed in 10%. In addition, pathological transfontanel USG results were present in 20%, and pathological cerebral MRI results in 22.5%. Seizures secondary to conditions capable of causing brain damage, particularly in the neonatal period, should be treated as quickly as possible, and a knowledge of avoiding the use of unnecessary antiseizure drugs is also essential. As with other neurological emergencies, it is very important to establish airway, respiration, and circulation. All our patients for whom seizures were determined and admitted to the neonatal ward for monitoring. In light of the monitoring of vital signs, the underlying etiology's diagnosis and therapy were prepared. Bedside blood glucose and electrolyte measurements should first be performed in case of all suspected seizures. Any hypoglycemia must be immediately corrected. However, if brief seizures secondary to other metabolic disorders such as hypocalcemia, hypomagnesemia, or hyponatremia, do not persist following seizure resolution, then no antiseizure drug should be used.

Neurological damage, mental impairment, muscular weakness, epilepsy, and personality disorders can all result from severe newborn hypoglycemia. Stomnaroska et al. described hypoglycemia as an important cause of neonatal mortality[14]. However, the current investigation did not find any mortality linked to hypoglycemia. Hyponatremia or hypomagnesemia was not observed, while 12.5% of our patients were found to experience hypocalcemia-related seizures.

Although pharmacological therapy options for neonatal seizures are increasing, phenobarbital remains the first-line agent of preference for the management of neonatal seizures worldwide. Phenobarbital is more effective than levetiracetam and easier to administer than

fosphenytoin and therefore continues to represent the basis of treatment. Emerging evidence has shown that it is safe for many neonates to discontinue phenobarbital once acute seizures have subsided and before discharge[15]. Besnili Acar D et al. evaluated patients who had convulsions in the neonatal period and stated that 30% of the 41 patients were started on a second antiseizure treatment. In the same study, it was reported that phenobarbital was most frequently used as the first-line treatment, and phenytoin was most frequently used as the second antiseizure[16]. In the current study, phenobarbital was also the antiepileptic medication that was used the most frequently. In addition, more than one drug can be used out of concern that undetected subacute seizures may sometimes damage the neonate brain despite initial treatment. Hirfanoğlu et al. described inadequate response to treatment and failure to respond to at least two antiepileptics as powerful independent parameters indicating a possibility of worsening seizure control and epilepsy[17]. Dual antiepileptics were required by 15% of the patient group in this study. Despite advances in neonatal care, the mortality rate among babies undergoing neonatal seizures is 20% remains at, with morbidity being seen in 65% of babies.

Early diagnosis and treatment of the seizure or underlying modifiable etiology is important since this can significantly reduce the scale of neonatal seizure-related morbidity[18]. Andreolli et al. reported an increased risk of epilepsy in patients presenting with neonatal seizures[19]. In the study reported by Yıldız et al., it was stated that there is a close relationship between Apgar score, need for resuscitation at birth, neonatal status epilepticus, cranial imaging findings, duration of antiepileptic treatment, and response to treatment given in the acute period and advanced neurodevelopmental findings[20]. The mortality rate for our patient group was 22.5%, which is in agreement with other research. Examination of our patients' post-discharge hospital records showed that the majority did not attend regular follow-ups, but that eight patients presenting to the pediatric neurology clinic were followed up with diagnoses of epilepsy, while one used no antiseizure drug. Among the patients who died, one patient had intracranial hemorrhage, four patients had preterm and low birth weight, two patients had hypoxia, and the etiology of two patients could not be determined. Among the patients who were followed up in the pediatric neurology outpatient clinic with a diagnosis of epilepsy, one patient was diagnosed with PLBB6 gene-related epilepsy (pyridoxine-dependent epilepsy), five patients were diagnosed with cerebral palsy and two other patients were under investigation with a prediagnosis of neurogenetic disease.

The retrospective nature, the small number of patients, hospital based study and not all patients had an EEG were the limitations of our study. Since our hospital was not fully equipped, the etiological diagnosis process was difficult due to the limitations of materials and some examinations (EEG, detailed genetic screening, etc.) and the cause of 15 patients could not be determined exactly. Information about the semiology and epileptic forms of seizures could not be accessed because the files contained insufficient information. In our study, term babies were more common than preterm babies. C/S delivery was more frequent in preterm babies and VD was more frequent in term babies. In addition, the mortality rate was higher in preterm than in term babies. Scans were sent from patients with suspected metabolic disease. The patient who was diagnosed with metabolic disease was diagnosed with pyridoxine-dependent epilepsy. Cerebral USG findings in preterm infants were consistent with periventricular leukomalacia.

CONCLUSION

In conclusion, among the known causes of neonatal convulsions, hypoxic-ischemic encephalopathy in term babies and germinal matrix bleeding in preterm babies were found to be the most common causes. However, despite extensive examinations and evaluations, the cause remains undetermined in a significant portion of cases. Long-term follow-up of newborns with convulsions is required to detect early neurodevelopmental problems that may develop during follow-up. Prospective studies in multi-centered and/or larger population-based case series are needed to obtain more detailed results.

Ethics Committee Approval: All procedures were by the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval for the study was obtained from the ethics committee of the hospital (No: 2022/3-30).

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