***Clinical Research***

# Evaluation of the Infants Who Had Seizure During Neonatal Period

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**ABSTRACT**

**Objective:** The purpose of this study was to determine etiological profile and neurodevelopmental prognosis of cases with seizures in neonatal period.
**Material and Method:** The medical records of 61 patients who were followed up for neonatal seizure in the pediatric neurology outpatient clinic were evaluated retrospectively.
**Results:** Risk factors were found in 59% of the patients. The most common risk factors were asphyxia (31.2%) and hypoglycemia (8.2%). The mean length of the follow-up duration for the patients was 13.97 ± 9.96 months. 18% patients were found to developed epilepsy. No significant relationship was found between development of epilepsy and birth weight, mode of delivery, presence of a risk factor, magnetic resonance imaging (MRI) findings, time of seizure onset, type of seizure, or having had status epilepticus (p >0.05). During the follow up, 6.6% patients were found to develop infantile spasms, and 3.3% patients developed cerebral palsy. Of the patients, 82% showed an age-appropriate development, 13.1% had global developmental retardation, and 4.9% had speech delay. No significant relationship was found between neuromotor development and the presence of risk factors, MRI findings, time of seizure onset, and seizure type (p >0.05). Neuromotor retardation was significantly more common among the patients who developed epilepsy (p <0.001).
**Conclusion:** Seizures are most common neurological problems of the neonatal period. The development of epilepsy in patients with seizures during neonatal period was found to be an important risk factor for neuromotor developmental retardation.

***Keywords:*** *Neonatal, Seizure, Epilepsy, Etiology, Prognosis.*

**ÖZET**

**Yenidoğan Döneminde Nöbet Geçiren İnfantların Değerlendirilmesi**

**Amaç:** Bu çalışmanın amacı yenidoğan döneminde konvülziyon geçiren olguların etiyolojik profilini ve nörogelişimsel prognozunu belirlemektir.
**Gereç ve Yöntem:** Çocuk nörolojisi polikliniğinde yenidoğan nöbeti tanısıyla takip edilen 61 hastanın tıbbi kayıtları retrospektif olarak değerlendirildi.
**Bulgular:** Hastaların %59'unda risk faktörü saptandı. En sık saptanan risk faktörü asfiksi (%31.2) ve hipoglisemi (%8.2) idi. Takip süresi ortalama 13.97 ± 9.96 aydı. Hastaların %18'inde epilepsi geliştiği saptandı. Doğum ağırlığı, doğum şekli, risk faktörü, manyetik rezonans görüntüleme (MRG) bulguları, nöbet başlangıç zamanı, nöbet tipi ve status epileptikus geçirme ile epilepsi gelişmesi arasında anlamlı bir ilişki saptanmadı (p >0.05). Takiplerinde %6.6 hastada infantil spazm ve %3.3 hastada serebral palsi geliştiği saptandı. Hastaların %82'sinde yaşa uygun gelişim, %13.1'inde global gelişme geriliği, %4.9'unda konuşma gecikmesi saptandı. Risk faktörü varlığı, MRG bulguları, nöbet başlangıç zamanı, nöbet tipi ile nöromotor gelişim arasında anlamlı bir ilişki saptanmadı (p >0.05). Epilepsi gelişenlerde nöromotor gerilik anlamlı olarak daha fazla bulundu (p <0.001).
**Sonuç:** Nöbetler yenidoğan döneminde en sık görülen nörolojik problemdir. Yenidoğan döneminde nöbet geçiren hastalarda epilepsi gelişmesi nöromotor gelişme geriliğinde önemli bir risk faktörüdür.

***Anahtar Sözcükler:*** *Yenidoğan, Nöbet, Epilepsi, Etiyoloji, Prognoz.*

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Neonatal seizures are one of the most common neurological problems in neonatal period. Despite the improvements in neonatal intensive care, estimated rates of seizures in full-term newborns are reported to be in the range of 1 to 3 per 1000 live births and have not changed significantly over the last two decades (1). In more than 80% of seizures, which appear to be the first sign of significant brain dysfunction, etiology is associated with an acute symptomatic cause and varies by gestational age. Hypoxic ischemic encephalopathy is a major cause in full-term newborns while intracranial bleeding is prominent among extremely preterm babies (2). Identification of etiology and the treatment of the seizures during the neonatal period are of great importance since they may lead to cognitive, intellectual, behavioral, and sensorimotor disorders (3).

In this study, 61 patients who were followed up in the pediatric neurology outpatient clinic were retrospec-

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tively evaluated in order to determine the etiology and prognosis of neonatal seizures.

## MATERIAL AND METHOD

The medical records of 61 patients who were followed up for neonatal seizure in the pediatric neurology outpatient clinic in 2012-2015 were evaluated retrospectively. The onset time of seizure, brain magnetic resonance imaging (MRI) findings, development of epilepsy, and neuromotor prognosis were evaluated along with their demographic data. Seizures were classified as subtle, clonic, tonic, and myoclonic based on the classification of Volpe (4).

The data were analyzed with SPSS (Statistical Package for Social Sciences) for Windows 19.0 (SPSS Inc., USA). Frequency distributions were presented as percentage, age in months, and values as mean ±standard deviation. Student *t* test was used to compare the two means and chi-square test was used to compare percentages. Spearman correlation analysis was used for correlations. A p value of < 0.05 was used for significance in all statistical tests.

## RESULTS

Demographic characteristics of the patients enrolled into the study were given in table 1.

***Table 1.*** *Demographic characteristics of the study sample.*

| Characteristics | | n | % |
|---|---|---|---|
| **Gender** | Male | 35 | 57.4 |
| | Female | 26 | 42.6 |
| **Male/Female** | 1.35 | | |
| **Delivery time** | Preterm | 9 | 14.8 |
| | Full-term | 52 | 85.2 |
| **Birth weight** | <1000 g | 2 | 3.3 |
| | 1000-1499 g | 1 | 1.6 |
| | 1500-2499 g | 6 | 9.8 |
| | ≥2500 g | 52 | 85.2 |
| **Mode of delivery** | Normal vaginal | 28 | 45.9 |
| | C/S | 33 | 54.1 |
| **Maternal age** | <20 years | 6 | 9.8 |
| | 21-35 years | 43 | 70.5 |
| | ≥36 years | 12 | 19.7 |

C/S: Cesarean section.

No significant relationship was found between development of epilepsy and gender, birth weight, mode of delivery, and maternal age (p >0.05).

Risk factors were found in 35 (57,4%) of the patients (Table 2).

***Table 2.*** *Distribution of risk factors.*

| Risk factors | n | % |
|---|---|---|
| HIE | 19 | 31.2 |
| Hypoglycemia | 5 | 8.2 |
| Intracranial hemorrhage | 4 | 6.6 |
| Sepsis | 4 | 6.6 |
| Bilirubin encephalopathy | 1 | 1.6 |
| Congenital CMV infection | 1 | 1.6 |
| Hypocalcemia | 1 | 1.6 |

HIE: Hypoxic ischemic encephalopathy, CMV: Cytomegalovirus.

The most common risk factors were asphyxia (31.2%) and hypoglycemia (8.2%). There were kinship between mother and father of 8 patients (13.1%).

Cranial MRI data was available for 44 (72.1%) of the patients; of these, 17 (38.6%) were normal. Cranial MRI results were given in table 3.

***Table 3.*** *Cranial magnetic resonance imaging findings.*

| Results | n | % |
|---|---|---|
| Normal | 17 | 38.6 |
| Porencephaly / periventricular white matter damage | 9 | 20.5 |
| Basal ganglia and/or thalamic lesions | 9 | 20.5 |
| Non-specific changes | 7 | 15.9 |
| Intracranial hemorrhage | 2 | 4.5 |

No relationship was found between the MRI findings and the development of epilepsy or the neuromotor developmental retardation.

Seizure characteristics of the patients were given in table 4.

***Table 4.*** *Seizure characteristics of the patients.*

| Characteristics | | n | % |
|---|---|---|---|
| **Time of seizure** | First 24 hour | 22 | 36.1 |
| | Day 1 to 7 | 23 | 37.7 |
| | > 7 | 16 | 26.2 |
| **Type of seizure** | Subtle | 35 | 57.4 |
| | Clonic | 14 | 22.9 |
| | Tonic | 9 | 14.8 |
| | Myoclonic | 3 | 4.9 |

Three patients (4.9%) had the history of status epilepticus. Ten patients (16.4%) who underwent metabolic screening were evaluated as normal.

The mean length of the follow-up duration was 13.97 ± 9.96 months . Nineteen (31.1%) patients were started on a single antiepileptic drug, and 13 (40.6%) were started on multiple antiepileptic drugs; antiepileptic medications of 29 patients (31.5%) had been withdrawn during the follow-up period. Eleven (18.0%) patients were found to developed epilepsy. No significant relationship was found between development of epilepsy and birth weight, mode of delivery, presence of a risk factor, MRI findings, time of seizure onset, type of seizure, or having had status epilepticus (p >0.05). Of those who developed epilepsy, 69.2% were taking multiple antiepileptic drugs. During the follow up, 4 (6.6%) patients were found to developed infantile spasms, and 2 (3.3%) patients developed cerebral palsy. Of the patients, while 50 (82%) showed an age-appropriate development, 8 (13.1%) had global developmental retardation, and 3 (4.9%) had speech delay. No significant relationship was found between neuromotor development and the presence of risk factors, MRI findings, time of seizure onset, and seizure type (p >0.05). Neuromotor developmental retardation was significantly more common among the patients who developed epilepsy (p <0.001). No infant death was observed in these patient sample.

## DISCUSSION

Seizures seen in the neonatal period are important since they can disrupt the integrity of the respiratory-circulatory system; besides, uncontrolled seizures cause serious brain damage and adversely affect the long-term prognosis. The convulsion threshold is lower in the immature brain than in the mature brain (3). While the incidence of seizures in full-term neonates is 1 to 3 per 1000 live births, it is reported to be 10 times higher in preterm newborns (1). Neonatal seizures have been reported to be more frequent among male infants (5). A naturally increased excitability was suggested in the neonatal period. The main reason for this is that glutamate, an excitatory neurotransmitter, is more excitatory, and gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, is less inhibitory (6). In experimental studies, it has been shown that the gender- and age-related maturation of the GABAergic system as well as the seizure control function of the substantia nigra pars reticulata were controlled by gonadal hormones and their metabolites (7). While having a birth weight of <1500 gr and male sex are risk factors in preterm babies, delivery by cesarean section and young maternal age were found to be the most important risk factors in full-term babies (1, 8, 9). In this study, 14.8% of the infants were preterm and 85.2% were full-term newborns. Risk factors were determined in 57.4% of the infants, and the most common risk factors were asphyxia (31.2%), hypoglycemia (8.2%), and intracranial hemorrhage (6.6%). Lower rate of intracranial hemorrhage was attributed to the fact that the number of preterm babies was lower in our study than other studies. In a study by Tekgul et al. (5), cerebral hypoxic-ischemic encephalopathy and intracranial hemorrhage were reported to be the most common risk factors. Andre et al. (10) reported the etiology of neonatal seizures which were asphyxia in 49.3% of the patients, infections in 24%, intracranial hemorrhages in 14.1%, and metabolic disorders in 5.6%.

It was reported that the risk of seizure was highest in the first 48 hours of the neonatal period (11). Another study showed that the highest risk of seizure was in the first postnatal 24 hours which was an indicator of poor prognosis (4). While the subtle seizure is the most common type of seizures in the neonatal period, and the tonic seizures are least frequent (3). In this study, time of seizure onset was the first 24 hours in 36.1% of the infants, and no significant relationship was found between the time of seizure onset and epilepsy. The most common type of seizure was subtle (57.4%), and the least common was myoclonic (4.9%). Myoclonic seizures are more frequent in pre-term than full-term infants (12). In this study 85% of the patients were full-term that may be the reason why myoclonic seizures are the least common. During the follow-up, epilepsy developed in 18.0% of patients, infantile spasm developed in 6.6% of patients and cerebral palsy developed in 3.3% of patients. In a study by Yıldız et al. (13), cerebral palsy was detected in 27.6%, epilepsy in 35.7%, and neurodevelopmental retardation in 50% of 112 newborns. Etiology, Apgar score, need for resuscitation at birth, neonatal status epilepticus, cranial imaging findings, type and duration of antiepileptic treatment, and response to acute treatment were reported to be strong prognostic factors for neurological outcomes. The incidence of epilepsy after neonatal seizures was detected 15.2% in a population-based study (14). It was reported that epilepsy had impact on the development of adverse neurological outcomes (15). In our study, developmental delay was more common among the patients who developed epilepsy ($p < 0.001$).

Neuroimaging is very helpful in determining the underlying etiology of neonatal seizures, especially in full-term babies. While transfontanelle ultrasonography is preferred in the initial acute phase, MRI should be preferred in advanced imaging since it is able to show posterior fossa lesions and migration disorders. In the study by Tekgul et al. (5), good clinical prognosis was observed in all of the patients with normal MRI findings and focal cortical damage. Poor clinical prognosis was observed in 63% of the patients with multifocal-diffuse cortical damage and deep gray matter lesion. In another study, diffuse severe MRI abnormalities were found to be associated with poor prognosis and death (16). In our study, approximately half of the patients had normal or non-specific changes findings in MRI. The most common pathologic findings were porencephaly, periventricular white, and gray matter damage; and no relationship was found between MRI findings and epilepsy or neuromotor developmental retardation.

In another study, 31% of the patients were reported to have cerebral palsy, 43% have to developmental retardation, and 32% have to epilepsy, and also seizure type, time of seizure onset, and fifth minute Apgar scores were reported to be independent predictors of cerebral palsy. The mode of delivery, time of seizure onset, and etiology were found to be determinants of developmental delay (17). Neonatal seizures were reported to have a high mortality risk of 10-35% during the neonatal period (18). The fact that no infant death was observed in our patient sample might be due to the evaluation of patients in the pediatric neurology outpatient clinic.

In conclusion, seizures are most common neurological problems of the neonatal period. The development of epilepsy in patients with neonatal seizures are an important risk factor for neuromotor developmental retardation. Because this is a single-center study with a small number of patients, there is need for multicenter studies to examine the risk factors for, and pathogenesis of long-term adverse neurodevelopmental outcomes following neonatal seizures.

**REFERENCES**


1. Rennie JM, Boylan GB. Seizure disorders of the neonate. In: Levene MI, Chervenak FA, editors. Fetal and Neonatal Neurology and Neurosurgery. 4th ed. Philadelphia: Elsevier 2009; 698-710.
2. Glass HC, Shellhaas RA, Wusthoff CJ et al. Contemporary profile of seizures in neonates: A prospective cohort study. J Pediatr 2016; 174: 98.
3. Glass HC. Neonatal seizures: advances in mechanisms and management. Clin Perinatol 2014; 41: 177-90.
4. Volpe JJ. Neonatal seizures. In: Volpe JJ, ed. Neurology of the Newborn. Philadelphia, PA: Saunders Elsevier; 2008: 203-44.
5. Tekgul H, Gauvreau K, Soul J et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006; 117: 1270-80.
6. Delorenzo RJ, Towne AF, Pellock JM et al. Increased seizure susceptibility of the immature brain. Dev Brain Res 1992; 33: 15-25.
7. Giorgi FS, Galanopoulou AS, Moshé SL. Sex dimorphism in seizure-controlling networks. Neurobiol Dis 2014; 72: 144-52.
8. Saliba R, Annegars FJ, Waller DK et al. Incidence of neonatal seizures in Haris County, Texas, 1992e1994. Am J Epidemiol 1999; 150: 763-9.
9. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. J Pediatr 1999; 134: 71-5.
10. Andre M, Matisse N, Vert P, Debruillec C. Neonatal seizures recent aspects. Neuropediatrics 1988; 19: 201-7.
11. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A et al. Electrographic seizure therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. J Child Neurol 2011; 26: 724-8.
12. Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005.
13. Yıldız EP, Tatlı B, Ekici B et al. Evaluation of etiologic and prognostic factors in neonatal convulsions. Pediatr Neurol 2012; 47: 186-92.
14. Andreolli A, Turco EC, Pedrazzi G, Beghi E, Pisani F. Incidence of epilepsy after neonatal seizures: a population-based study. Neuroepidemiology 2019; 52: 144-51.
15. Oh A, Thurman DJ, Kim H. Independent role of neonatal seizures in subsequent neurological outcomes: a population-based study. Dev Med Child Neurol 2019; 61: 661-6.
16. Michael J. Neonates with seizures: What predicts development? J Child Neurol 2012; 27: 1022.
17. Garfinkle J, Shevell MI. Cerebral palsy, developmental delay, and epilepsy after neonatal seizures. Pediatr Neurol 2011; 44: 88-96.
18. Uria-Avellanal C1, Marlow N, Rennie JM. Outcome following neonatal seizures. Semin Fetal Neonatal Med 2013; 18: 224-32.



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