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Clinical and Electrophysiological Evaluation of Neonatal Seizures

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Abstract

Neonatal seizures are the most prevalent and distinctive sign of neurologic dysfunction in early-life. In spite the recent advances in medical care and technology in newborn intensive care units (NICU), it remains an important clinical issue of diagnosis, treatment, and prognosis. This was a retrospective, observational cohort study of neonates with seizures treated in the Ondokuz Mayıs University Faculty of Medicine NICU. Demographics of the babies, risk factors and etiology of seizure, type of clinical seizure, electroencephalographic and radiological findings, and anti-seizure treatments were recorded. The incidence of neonatal seizures was 4.5% in NICU admissions. Seventy-two babies with seizures included, 69,4% were diagnosed with electroclinical seizures. The most common seizure types were clonic (35.8%) and motor automatisms (32.8%). Perinatal asphyxia/hypoxic ischemic encephalopathy (HIE) (29.2%) was the most common etiological factor, whereas hypoglycemia was the most common metabolic problem (15.3%). Eighty-one percent of seizures due to HIE were observed in the first 48 h. Hyperbilirubinemia (kern icterus), hypocalcemia, and idiopathic neonatal convulsions were observed after the first 48 h. Abnormal findings were detected in 76.4% of electroencephalographies obtained during the neonatal period. Phenobarbital was the first-line therapy in 98.6% of babies, and 83.3% of the infants were seizure-free with phenobarbital. Seizures are common in the neonatal period and may be associated with significant brain damage. Seizures appear as an important symptom of the underlying pathology and not as a disease.

Keywords: Neonatal seizures, electroencephalography, motor automatism, perinatal asphyxia, phenobarbital

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Introduction

Although neonatal seizures are one of the most common reasons for admission to neonatal intensive care units (NICU), there are still controversies regarding their management. The main reason for this is the inconsistency between clinical and electroencephalographic (EEG) findings. While some motor phenomena that are accepted as seizures by clinical observation are not accompanied by EEG changes (clinical seizure), it is also possible to observe unexpected and frequent EEG changes (electrographic seizure) in long-term video EEG recordings of high-risk newborns without any motor phenomenon. However, seizures with correlated clinical and EEG findings (electroclinical seizures) can also be observe in newborns.[1] According to motor findings, seizures were generally defined as focal clonic, multifocal clonic, generalized tonic, myoclonic, and motor automatisms. Motor automatisms (subtle seizures), the most common seizure form, are usually without an electrographic correlate, can be triggered by stimuli, and present as abnormal eye movements, mouth smacking, swimming, or pedaling movements that do not conform to common semiology. Non-epileptic paroxysmal events are also common in this age group and may be difficult to distinguish from seizures at times.[2,3]

Almost 85% of seizures are symptomatic, and early and accurate diagnosis of the specific underlying etiology is critical. Most seizures have an acute symptomatic etiology such as hypoxic ischemic encephalopathy (HIE), vascular causes, acute metabolic disorders, and central nervous system (CNS) infections, and these seizures are usually self-limited and treatable. Some neonatal seizures are due to genetic origin, congenital viral infections, and brain malformations, and seizures originating from indirect symptomatology are more resistant and require long-term treatment.[4]

The aim of this study was to retrospectively evaluate the clinical, electrophysiological, and imaging results of newborns hospitalized in the NICU for seizures or who had seizures during their NICU stay and to determine the relationships between etiology, physical examination, and treatment.

Materials and Methods

This was a retrospective study of newborns admitted, evaluated, and treated in Ondokuz Mayıs University Medical Faculty Children's Hospital NICU due to seizures or had seizures during their stay between June 1, 2013 and March 31, 2015. The babies were evaluated metabolically and by EEG, cranial magnetic resonance imaging (MRI), and transfontanel ultrasonography (TFUS).

Patients were classified after birth by calculating their corrected age at 37 weeks for preterm births and within the first month for term births. Therefore, patients whose EEG was not performed within the first 30 days (in the neonatal period) after 37 weeks according to their term or adjusted age were excluded from the study.

Neonatal EEGs were evaluated in terms of basic activity, taking into account the conceptional age. Accordingly, EEG findings were classified as normal, slightly increased sharp wave discharges, increased sharp wave discharges and immaturation, burst suppression, and low amplitude.

Information about the first seizure time and the clinical type of seizure was recorded from patient files. Patients were grouped as babies who had seizures in the first 48 h after birth and those who had seizures after 48 h. Seizures were classified according to Volpe, which is based on clinical features, as motor automatism (subtle), clonic, tonic, and myoclonic seizures, during the study period.[5] Serum glucose levels below 47 mg/dL were defined as hypoglycemia, and serum total calcium concentrations below 8 mg/dL in term infants and below 7 mg/dL in preterm infants were defined as hypocalcemia.[6]

Perinatal asphyxia/HIE was evaluated according to the American College of Obstetricians and Gynecologists (ACOG) criteria: Cord blood pH <7, base deficit >16 mmol/L, neonatal encephalopathy and seizures, and 5th minute Apgar score <3 was considered as severe fetal asphyxia.[7] Mild, moderate and severe HIE diagnoses were evaluated according to the Thompson scoring system. Those with a Thompson score of ten or less were classified as mild, those with 11-14 points as moderate, and those with higher were classified as severe HIE.[8] The Ethics Committee of Ondokuz Mayıs University Non-Interventional Clinical Research approved the study (no: 2015/173, date: 27.03.2015).

Statistical Analysis

In the analysis of the data, in addition to descriptive statistics, chi-square and Fischer exact tests for group comparisons of categorical variables were used. The results were evaluated with a 95% confidence interval and significance level of $p<0.05$. The IBM SPSS Statistics Version 22.0 package program was used for statistical analysis of the data.

Results

One thousand six hundred four babies were admitted to the NICU during the study period, and data of 96 patients with suspected seizures were retrospectively analyzed. Sixteen babies (16.6%) were hospitalized for investigating the seizure etiology, and 80 (83.4%) were hospitalized for other reasons but had seizures during their NICU stay. Twenty-four patients were excluded from the study because of the diagnosis of benign non-epileptic movements, mainly benign sleep myoclonus, and 72 babies were eventually included in the study.

The incidence of neonatal seizures was 4.5% in NICU admissions. 43 (59.7%) of the patients were boys, 45 (62.5%) were term infants, and 56 (77.8%) were born by cesarean section. The average birth weight was 2791 (840-4700) grams, and the average gestational age was 36.5±3.36 ($27^{6/7}$-42) weeks.

Sixty-seven patients had clinical seizures and five patients had epileptiform EEG changes without clinical correlation (electrographic seizures). No EEG abnormality was detected in 17 (25.4%) patients who had clinical seizures and were classified as clinical only

seizures, whereas the remaining 50 (74.6%) patients had coexistence of seizures and EEG abnormalities and were classified as electroclinical seizures.

When 67 patients with clinical seizures were classified according to the time of seizure onset, 23 (34.7%) infants presented with seizures in the first 48 h and 44 (65.3%) after 48 h (**Table 1**). Treatment was started in five patients without clinical seizures because they had EEG findings.

According to the gestational age, 23 patients had clinical seizures before 37 weeks, and the most common seizure type was clonic seizures in 11 (47.9%), motor automatisms in 7 (30.4%), tonic type in 2 (8.7%), tonic+clonic type in 2 (8.7%) and tonic+myoclonic type in 1 (4.3%) patient. According to the gestational age, in 44 patients who had clinical seizures after 37 weeks, the most common seizure type was motor automatisms in 15 (34.2%), whereas clonic type was observed in 13 (29.5%), tonic type in 8 (18.2%), tonic+clonic type in 6 (13.6%), and tonic+myoclonic type in 2 (4.5%) patients (**Table 2**).

In 60 (83.3%) babies, phenobarbital alone was the first-line anticonvulsive treatment, and seizure control was achieved. In eleven patients, levetiracetam and/or valproic acid and vigabatrin were added to phenobarbital treatment to control resistant seizures (**Table 3**).

TFUS was performed in 69 (95.8%) patients, and 49 (71%) patients were evaluated as normal. In 20 (29%) babie, abnormalities were found in TFUS, including intracranial hemorrhage (ICH) in 9 (13%), hydrocephalus in 6 (8.7%), cystic encephalomalacic changes in 3 (4.3%), meningitis in 1 (1.4%), and sinus vein thrombosis in 1 (1.4%).

54 (75%) patients underwent cranial MRI, of which 19 (35.2%) were reported as normal. Abnormalities were found in the cranial MRIs of the remaining 35 (64.8%) babies. These were: Intracranial hemorrhage in 8 (14.8%) patients,increase in extra-axial CSF distance in 6 (11.1%), cystic encephalomalacic changes in 6 (11.1%), hydrocephalus in 5 (9.3%), basal ganglia involvement in 2 (3.7%), cerebral dysgenesis in 2 (3.7%), meningitis in 1 (1.9%), sinus vein thrombosis in 1 (1.9%), tuberous sclerosis in 1 (1.9%), microcephaly in 1 (1.9%), polymicrogyria in 1 (1.9%), and myelination disorder in 1 (1.9%) patient.

When etiologies for neonatal seizure were considered, perinatal asphyxia/HIE was the most common factor (29.2%). Transient metabolic disorders were found in 20.8% of the patients, cerebral developmental abnormalities in 16.8%, intracranial hemorrhage, hematoma, and thrombosis in 12.5%, and sepsis/meningitis in 12.5%. Five patients had bilirubin-induced encephalopathy (BIE). Etiology could not be uncovered in one patient (1.4%) despite all investigations (**Table 4**).

When 67 patients with clinical seizures were classified according to the etiology of the seizure type, 2 of 8 patients with metabolic disease had concomitant tonic myoclonic seizures, two had tonic-clonic seizures, two had clonic seizures, 1 had subtle seizures, and 1 had

Highlights

- Neonatal seizures may be associated with significant brain damage, appear as an important symptom of the underlying pathology, not as a disease.
- Motor automatism type seizures were the most frequent type of seizures in hypoxic ischemic encephalopathy.
- The efficacy of phenobarbital is much higher than levetiracetam.
- The findings of cranial magnetic resonance imaging and transfontanel ultrasound were highly overlapped.
- When myoclonic seizures are observed, the clinical course will be more severe and there may be resistance to treatment.

Table 1. *Clinical characteristics of the patients (n=72)*

	Number of patients (n)	Percentage (%)
Gender		
Boy	43	59.7
Girl	29	40.3
Time of delivery		
Term	45	62.5
Premature	27	37.5
Mode of delivery		
Cesarean	56	77.8
NSVD	16	22.2
Birth weight (grams)		
>2.500 g	47	65.3
1.500-2.499 g	15	20.8
<1.500 g	10	13.9
Onset of first seizure (n=67)		
First 48 h	23	34.3
After 48 h	44	65.7

NSVD: Normal spontaneous vaginal delivery

Table 2. *Distribution of clinical seizure types by time of birth (n=67)*

Seizure types	Time of birth			
	Premature		Term	
	Patients (n=23)	(%)	Patients (n=44)	(%)
Motor automatism	7	30.4	15	34.2
Clonic	11	47.9	13	29.5
Tonic	2	8.7	8	18.2
Tonic+clonic	2	8.7	6	13.6
Tonic+myoclonic	1	4.3	2	4.5

Table 3. *Distribution of patients according to the anti-seizure drugs used*

Drugs used in the treatment	Number of patients (n)	Percentage (%)
Phenobarbital	60	83.3
Levetiracetam	1	1.4
Phenobarbital + levetiracetam	9	12.5
Phenobarbital + levetiracetam + vigabatrin	1	1.4
Phenobarbital + levetiracetam + valproic acid	1	1.4
Total	72	100

tonic seizures. Seizures in the form of motor automatism were observed more frequently in patients with idiopathic neonatal seizures and perinatal asphyxia, clonic seizures were observed more frequently in patients with hypoglycemia or sepsis, and tonic seizures were observed more frequently in patients with hypocalcemia.

When patients were classified according to the time of seizure, BIE, hypocalcemia, idiopathic neonatal convulsion, and sepsis-related seizures were observed after the first 48 h, whereas most seizures due to HIE were observed in the first 48 h. Most patients with hypoglycemia, ICH, and cerebral developmental abnormalities also had seizures after the first 48 h (**Table 5**).

Table 4. *Distribution of neonatal seizures according to the etiological causes*

Etiological causes	Number of patients (n)	Percentage (%)
Perinatal asphyxia/HIE	21	29.2
Transient metabolic disorders	15	20.8
Hypoglycemia	11	15.3
Hypocalcemia	4	5.5
Cerebral developmental abnormalities	12	16.7
Cerebral dysgenesis	4	5.5
Hydrocephalus	3	4.2
Microcephaly	2	2.8
Agenesis of the corpus callosum	1	1.4
Tuberous sclerosis	1	1.4
Polymicrogyria/pachygyria	1	1.4
Intracranial hemorrhage/hematoma/thrombosis	9	12.5
ICH	6	8.3
Subdural hematoma	2	2.8
Sinus vein thrombosis	1	1.4
Hyperbilirubinemia/kernicterus	5	6.9
Sepsis/meningitis	9	12.5
Unknown cause	1	1.4
Idiopathic neonatal convulsion	1	1.4
Total	72	100

HIE: Hypoxic ischemic encephalopathy

When the patients with seizures were evaluated according to EEG findings: In 22 babies with subtle seizures, EEG was normal in 22.7%, slightly increased sharp wave discharges were observed in 45.5%, and increased sharp wave discharges and immaturation were found in 31.8%. In 24 patients with clonic seizures, normal EEG findings were observed in 37.5%, slightly increased sharp wave discharges were observed in 25%, and increased sharp wave discharges and immaturation findings were observed in 37.5%. In 10 patients with tonic-type seizures, normal EEG findings were observed in one (10%) and increased sharp wave discharges were observed in the rest (90%). Burst suppression and low amplitude findings in EEG were observed only in patients with tonic and myoclonic seizures, and normal EEG findings were not observed in patients with this type of seizure (**Table 6**).

There was no significant association between gender, term/preterm birth, mode of delivery, birth weight, seizure type, EEG findings, and seizure etiology ($p>0.05$). Compared with infants with metabolic and other etiological causes, the incidence of seizures in the first 24 h was significantly higher in the perinatal asphyxia group ($p<0.01$).

Discussion

Because of the high morbidity and mortality of neonatal seizures, it is necessary to conduct studies in this area. Early recognition of newborn seizures and performing emergency interventions, identification of valuable prognostic factors in long-term follow-up by determination of prenatal, natal, and postnatal risk factors, and evaluation of treatment methods and duration are the main objectives.

In our study, seizures occurred after 48 h of life in 65.3% of the patients, regardless of the etiology. In many studies, it has been emphasized that seizures are mostly of the subtle type and occur in the first 12-24 h in patients with HIE.[5,9] In our series, seizures were observed within the first 48 h in 81% of the babies with HIE, and motor automatism was the most common seizure type.

When the seizure types of our patients were examined, mostly clonic (35.8%) and subtle type (32.8%) seizures were observed. These were followed by multiple seizure

Table 5. *Distribution of etiology of seizures according to seizure type and time*

	Seizure type					Seizure time	
						First 48 h	After 48 h
Etiology of seizure	Subtle n (%)	Clonic n (%)	Tonic n (%)	T+C n (%)	T+M n (%)	n (%)	n (%)
Idiopathic neonatal convulsion	1 (100)	0 (0)	0 (0)	0 (0)	0 (%0)	0 (%0)	1 (100)
ICH	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	0 (0)	2 (33.3)	4 (66.7)
Perinatal asphyxia/HIE	11 (52.4)	2 (9.5)	2 (9.5)	5 (23.8)	1 (4.8)	17 (81)	4 (19)
Hypocalcemia	0 (0)	1 (25)	3 (75)	0 (0)	0 (0)	0 (0)	4 (100)
Hypoglycemia	3 (27.3)	6 (54.5)	0 (0)	0 (0)	2 (8.2)	3 (27.3)	8 (72.7)
Hyperbilirubinemia/kernicterus	1 (20)	2 (40)	2 (40)	0 (0)	0 (0)	0 (%0)	5 (100)
Cerebral developmental abnormalities	2 (25)	3 (37.5)	2 (25)	1 (12.5)	0 (0)	2 (25)	6 (75)
Subdural hematoma	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Sepsis/meningitis	3 (33.3)	6 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	9 (100)

HIE: Hypoxic ischemic encephalopathy, ICH: Intracranial hemorrhage, T+C: Tonic+clonic, T+M: Tonic+myoclonic

Table 6. *Evaluation of EEG findings according to seizure type*

	Seizure type				
EEG findings	**Subtle**	**Clonic**	**Tonic**	**Tonic+clonic**	**Tonic+myoclonic**
Normal	5 (22.7)	9 (37.5)	1 (10.0)	2 (25.0)	0 (0.0)
Slightly increased sharp wave discharges	10 (45.5)	6 (25.0)	8 (80.0)	1 (12.5)	1 (33.3)
Increased sharp wave discharges and immaturation	7 (31.8)	9 (37.5)	1 (10.0)	5 (62.5)	1 (33.3)
Burst suppression and low amplitude	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)

EEG: Electroencephalographic

types (16.4%) and tonic seizures (14.9%). The type of seizure observed is related to the etiological cause. Tonic seizures are more common in patients with severe cerebral dysfunction and hypocalcemia.[1] In our series, 66.7% of the seizures caused by infection were of the clonic type. Studies have reported different results for the frequency of seizure types. Mizrahi and Clancy[10] reported that subtle seizures were more common than other seizure types. Similarly, Scher[11] evaluated 62 term and 30 preterm infants in their study and reported that subtle seizures were the most common type of seizure in both groups, and the distribution of clonic, myoclonic, and tonic seizures was almost equal. Tekgul et al.[12] reported that clonic (64%) seizures were observed most frequently, followed by tonic (19%), subtle (13%), and myoclonic (7%) seizures. Pisani et al.[4] grouped the cases as those with one type of seizure and those with more than one type of seizure, and reported that the number of patients in the second group doubled the number of patients in the first group. Similarly, Ronen et al.[13] also found that cases experiencing more than one type of seizure were the most common. In our study, we observed that one-third of the patients had clonic seizures. Although this result is compatible with literature data, the diagnosis of almost all seizures in preterm and term newborns only by clinical observation in NICUs and the possibility of different interpretations of clinical seizure types by physicians who are following the patients suggest that more reliable data can be obtained with long-term video-EEG monitoring.

Perinatal asphyxia/HIE is the most common clinical condition known to cause acute neurological disorders and seizures in the neonatal period.[14,15] The incidence of perinatal asphyxia causing seizures was around 30% in the late 1960s, and then increased to current rates, which is 40-45%.[16] Although only patients with EEG recordings were included in our study, perinatal asphyxia/HIE was found to be the most common cause of neonatal seizures (30.5%), which was compatible with the literature. Intracranial hemorrhage is responsible for 12.5% of etiological causes. The most common cause of intracranial hemorrhage is prematurity.

In our study, the incidence of transient metabolic disorders in seizures was 20.8%. The most common metabolic disorder that can cause severe sequelae in the neonatal period is hypoglycemia. In particular, babies with low birth weight and low gestational age and infants of diabetic mothers are at high risk. Volpe reported the frequency of seizures due to isolated hypoglycemia without any other metabolic defect to be 9%.[5] In the study by Kumar et al., the frequency was 11.1% and the median time of seizures was 63.5 h.[17] Similarly, in our study, seizures were observed after the first 48 h in 72.7% of the hypoglycemic cases. Studies showing EEG findings in hypoglycemic seizures are limited. However, the rate of abnormal EEG accompanying hypoglycemic seizures has been reported in a very wide range in studies on neonatal seizures. While this rate was 42.9% in the study by Arhan et al.[18] reported this rate as 88.8%. In this study, abnormal EEG findings were observed in 7 of 11 patients (63.6%) with hypoglycemic seizures.

Hypocalcemia was the etiology of seizures in four patients (5.5%s) and BIE was the etiology of seizures in five patients (6.9%). Of these five babies with severe hyperbilirubinemia, two were treated only with phototherapy and three had exchange transfusion followed by phototherapy. The first neurological manifestations of BIE are poor sucking, lethargy, opisthotonus, and high-pitched cry. Early encephalopathy findings may be confused with sepsis, asphyxia, and hypoglycemia. The development of neurological complications in the early period indicates a poor prognosis.[19] In our study, hypotonia, poor sucking, lethargy, and seizures were the major abnormal neurological findings in patients with BIE.

Abnormal findings were detected in 76.4% of EEGs taken during the neonatal period. Slightly increased sharp wave discharges were observed in 31 (43.1%) patients, increased spike wave discharges and immaturation in 23 (31.9%) patients, and burst suppression and low amplitude findings were observed in 1 patient (1.4%). When these EEGs were evaluated according to the seizure type, we observed that myoclonic seizures did not have normal EEG findings and progressed with severe clinical and EEG findings (burst suppression), whereas subtle, tonic, clonic, and tonic/clonic seizures had a milder clinical course and EEG findings. In addition, we argue that continuous EEG recording is necessary in suspicious cases because there may be electrographic seizures only that can be diagnosed electrographically.

We also evaluated cranial imaging findings based on TFUS and cranial MRI. Intracranial hemorrhage was detected in 9 of 69 patients who underwent TFUS and in 8 of 54 patients who underwent cranial MRI. The advantages of TFUS such as easy accessibility, ease of application at the bedside, and non-invasiveness have been proven in many studies.[20] Therefore, TFUS is the first-line imaging study for neonatal seizures in the NICU. Leijser et al.[21] compared the cranial US findings of babies born before 32 weeks gestational age that were obtained in the neonatal period with the MRI images taken after the 40th gestational week and showed that the US findings overlapped with MRI findings, especially in recognizing periventricular, intraventricular, and intraparenchymal lesions. In our study, it was also

observed that the findings of cranial MRI and TFUS were highly overlapping. Wang et al.[22] evaluated the cranial MRI findings of 24 infants (two preterm and 22 term) aged 6-18 days with hyperbilirubinemia and kernicterus symptoms and reported that an increase in signal intensity in the basal ganglia and thalamus is rare in T2-weighted MRI images taken during the acute phase of kernicterus. All five cases in our study were term newborns, and an increase in signal intensity was observed in the basal ganglia and thalamus on T2-weighted images in the acute period in two of them.

The decision about the duration of treatment in cases with neonatal seizures should be made by considering the risk of recurrence after discontinuation of anti-seizure treatment and the side effects of the current treatment.[23,24] To date, no satisfactory study has been conducted regarding the appropriate duration of use and withdrawal of drugs, and specific principles have not been established.[10,16] Although a very common problem, there are few randomized controlled trials with anti-seizure drugs such as phenobarbital, phenytoin, benzodiazepines, and levetiracetam, which limits the treatment options in neonatal seizures.[1,25,26] Sharpe et al.[27] stated that the efficacy of phenobarbital is much higher than that of levetiracetam, which has a better side effect profile and is being used frequently. In our study, seizures were controlled with phenobarbital in 83.3% of infants. Similarly, in the study by Pisani et al.[4], 53.7% of the patients had a rapid response to treatment. Regarding response to antiepileptic medications, 84.7% of the study group achieved antiepileptic treatment and seizure control, whereas 14.3% did not and were switched to combined antiepileptic treatment.

Study Limitations

One of the important limitations of our study is the inability to conduct genetic studies for etiology, especially for channelopathies, in cases of unknown cause or in those with resistant seizures. Another limitation is that the study was conducted before therapeutic hypothermia was available in the NICU. The lack of long-term follow-up is another limitation. Therefore, no clear conclusion can be drawn regarding the course and prognosis of these cases.

Conclusion

Seizures, which are common in the neonatal period and may be associated with significant brain damage, appear as an important symptom of the underlying pathology and not as a disease. HIE is the most common cause of neonatal seizures. Although the incidence of HIE has decreased due to advances in obstetrics and fetal monitoring in recent years, it still holds in the first place. Subtle-type seizures were the most frequent type of seizures in babies with HIE. Therefore, it appears that perinatal asphyxia/HIE and metabolic disease should be considered in the etiology of seizures observed in the first 2 days of life, while CNS developmental disorders, infections, and transient metabolic disorders should be investigated in seizures that occur after the first 2 days. When the EEGs were evaluated according to the type of seizure, it was found that myoclonic-type seizures did not have normal EEG findings and progressed with severe clinical and EEG findings (burst suppression), whereas subtle, tonic, clonic, and tonic/clonic seizures had a milder clinical course and EEG findings. Therefore, it should be kept in mind that when myoclonic seizures are observed, the clinical course will be more severe and there may be resistance to treatment.

Ethical Approval: The Ethics Committee of Ondokuz Mayıs University Non-Interventional Clinical Research approved the study (no: 2015/173, date: 27.03.2015).

Informed Consent: Written informed consent was obtained from the patients/ guardians.

Author Contributions: Aykanat MA: Surgical and Medical Practices, Design, Data Collection or Processing, Literature Search, Writing, Akça Ü: Concept, Design, Analysis or Interpretation, Literature Search, Writing, Akça G: Design, Analysis or Interpretation, Seren HC: Surgical and Medical Practices, Data Collection or Processing, Özyürek H: Concept.

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