

RISK FACTORS FOR SEIZURE RECURRENCE IN CHILDREN FOLLOWING AN UNPROVOKED SIZURE

Uyarılmamış Nöbet Sonrasında Çocuklarda Nöbet Tekrarı İçin Risk Faktörleri

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ABSTRACT

Objective: The aim of this study was to identify the risk factors for seizure recurrence in children who have experienced an unprovoked seizure and have normal sleep electroencephalogram (EEG). **Method:** The study population included 80 children who presented with first unprovoked seizure and had normal sleep EEG in the first week of the seizure. Demographic data and characteristics of the seizure were recorded from patient files. Patients were evaluated for seizure recurrence at the first year of the initial seizure and classified into two groups: Group 1 (no seizure recurrence) and Group 2 (seizure recurred). **Results:** The study population comprised 80 patients. The mean age at presentation was 82.3 ± 56.1 months. The first seizure type was generalized in 77.5% of the patients, with a mean seizure duration of 5 minutes. Group 2, consisted of 35 patients (44%) who had seizure recurrence during the first year. Seizure recurrence was within the first 6 months in 29 (83%) of the patients. There was no significant difference in terms of age, gender, consanguinity, birth history, mental development, presence of seizure or epilepsy in the family, seizure type, seizure duration, seizure occurring at sleep or awake time, and the number of seizures in the first 24 hours and cranial imaging findings between group 1 and group 2. **Discussion:** Following a first unprovoked seizure, we could not find any risk factor for recurrence of the seizure in the children who have normal EEG evaluation. We suggest larger series and extended follow-up will be helpful to identify the risk factors for recurrence in this population.

Keywords: Electroencephalogram, Epilepsy, Seizure

ÖZET

Amaç: Bu çalışmanın amacı, uyarılmamış nöbeti olan ve uyku elektroensefalogram (EEG) incelemesi normal olan çocuklarda nöbet tekrarı açısından risk faktörlerinin belirlenmesi **Yöntem:** Çalışma grubuna ilk uyarılmamış nöbet ile başvuran ve nöbetin ilk haftasında uyku EEG si normal olan 80 çocuk dahil edildi. Demografik bilgi ve nöbet özellikleri hasta dosyalarından kaydedildi. Hastalar, ilk nöbetin 1. yılında nöbet tekrarı açısından değerlendirildi ve iki grupta sınıflandırıldı: Grup 1 (nöbeti tekrarlamayan) ve Grup 2 (nöbet tekrarı olan). **Bulgular:** Çalışma grubu 80 hastadan oluştu. Ortalama yaş $82,3 \pm 56,1$ ay idi. İlk nöbet tipi hastaların %77,5'inde jeneralize idi. Ortalama nöbet süresi 5 dk idi. Grup 2, ilk yılda nöbet tekrarı olan 35 hastadan (%44) oluşmakta idi. Nöbet tekrarı, 29 (%83) hastada ilk 6 ay içerisinde idi. Yaş, cinsiyet, akrabalık, doğum öyküsü, mental gelişim, ailede nöbet veya epilepsi öyküsü, nöbet tipi, nöbet süresi, nöbetin uykuda ya da uyanık olması, ilk 24 saatte nöbet sayısı ve kranial görüntüleme bulguları açısından grup 1 ve grup 2 arasında anlamlı fark bulunmadı. **Tartışma:** İlk unprovoked nöbeti takiben, EEG incelemesi normal olan çocuklarda nöbet tekrarı açısından herhangi bir risk faktörü bulamadık. Daha geniş seriler ve daha uzun izlem süresinin bu grupta nöbet tekrarı için risk faktörlerini belirlemede faydalı olacağını düşünüyoruz.

Anahtar Kelimeler: Electroencephalogram, Epilepsi, Uyarılmamış nöbet

INTRODUCTION

Seizure is a transient clinical condition which is caused by abnormal, excessive, and synchronized discharge of a group of neurons. This discharge results in abnormal motor movements, sensory disturbances, automatisms, and changes in the level of consciousness (Falco-Walter et al., 2018; Fisher et al., 2005; Stafstrom & Rho, 2017; Shinnar et al., 1996). A seizure is considered unprovoked when no causative factor can be identified in the absence of infections, trauma, or metabolic or toxic disturbances that could affect the brain. To consider a diagnosis of epilepsy, there must be at least one seizure and at least a 60% risk of recurrence in 10 years' time (Falco-Walter et al., 2018). EEG abnormality is an important risk factor for the recurrence of seizures (Chen et al., 2024; Takami & Nakagawa, 2021). In this study, we investigated the children who have experienced an unprovoked seizure and have normal EEG and evaluated the risk factors which can have a potential effect on the recurrence of seizures other than EEG. Follow-up of these children and investigation of the risk factors will be helpful to discriminate the population who will develop epilepsy earlier.

METHOD

The study was done as a pediatric thesis in 2009 in a single center at Ankara Dr. Sami Ulus Child Health and Diseases Education and Research Hospital, retrospectively. It involved 80 children who were followed up in the pediatric neurology unit with a first unprovoked seizure and who had normal sleep EEG evaluation in the first week of the seizure. Seizure type was defined based on International League Against Epilepsy (ILAE) criteria; having more than one seizure in the first 24 hours is accepted as one seizure (Fisher et al., 2005). Sleep EEG were recorded during the first week following the seizure and analyzed in standard protocols. Patients with febrile seizures, symptomatic seizures (metabolic, infectious), who have epilepsy diagnose or started on antiepileptics were excluded. Demographic data (age, gender, consanguinity, birth history (birth weight, type of delivery, postnatal hospitalization), mental development, family history of seizure and

epilepsy), seizure characteristics (type, duration, timing of the first seizure; at sleep or at awake time, occurrence of more than one seizure in the first 24 hours, time interval between the first seizure and second seizure in the seizure recurrence group), neuroimaging (computerized tomography (CT)/magnetic resonance (MRI)) findings, and neurological examination results were retrieved from patient files. Patients were classified into two groups according to seizure recurrence within 1 year, group 1 (who had no seizure recurrence) and group 2 (who had seizure recurrence).

Statistical Analysis:

Statistical analysis was performed using SPSS 2009, Shapiro–Wilk test was used to evaluate the distribution of the variables. Student t test or Mann-Whitney U test were used to analyze continuous variables. Pearson's Chi-squared test or Fisher's exact test were used to analyze nominal variables. Univariate logistic regression analysis was used to calculate odds ratio (OR) and 95% confidence interval (CI) for the risk factors to predict seizure recurrence. Multivariate logistic regression analysis was performed for the results of $p < 0.25$. Stepwise Logistic Regression Analysis was performed to identify the most predictive factors for seizure recurrence and values of $p < 0.05$ was accepted statistically significant.

RESULTS

The study involved 80 patients, comprising 46 males (57.5%) and 34 females (42.5%). Group 1, consisted of 45 patients and group 2 consisted of 35 patients. The mean age at presentation was 82.3 ± 56.1 months (range: 9-192 months). Five patients (6.3%) were less than 1 year, 13 patients (16.3%) were between 1-2 years, 21 patients (26.3%) were between 3-6 years, and 41 patients (51.3%) were older than 6 years. There was consanguinity in 17.8% in Group 1 and 14.3% in Group 2 ($p = 0.67$, $OR = 0.77$). The mean birth weight was similar, 3148 ± 758 grams in Group 1 and 3288 ± 628 grams in Group 2. The ratio of delivery by cesarean section was 24.4% in Group 1 and 28.6% in Group 2 ($p = 0.67$, $OR = 1.24$). Postnatal hospitalization was 22.2% in Group 1 and 8.6% in Group 2 ($p = 0.10$, $OR = 0.33$). Mental development

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was reported abnormal in 8.9% of Group 1 and in 8.6% of Group 2 ($p=1.00$, $OR=0.96$, 95% CI: 0.2-4.6). Family history of epilepsy was 17.8% in Group 1 and 31.4% in Group 2 ($p=0.15$, $OR=2.12$, 95% CI: 0.7-6). Family history of febrile convulsions was 26.7% in Group 1 and 22.9% in Group 2 ($p=0.69$, $OR=0.81$). Seizure type was generalized in 62 patients (77.5 %), focal in 10 patients (12.5 %), combined generalized and focal in 4 patients (5%) and not identified in 4 patients (5%). First seizure occurred at sleep in 40 patients (50%) and at awake time in 40 patients (50%). The mean duration of the seizure was 5 minutes and 12 patients (15%) had more than one seizure in the first 24 hours. During the first year, 45 patients (56.2%) had no seizure recurrence, classified as group 1, while 35 patients

(43.8%) had seizure recurrence, classified as group 2. The age at first seizure was 80.1 ± 52.8 months in Group 1 and 85.2 ± 60.7 months in Group 2 ($p=0.78$). The male/ female ratio was 1.36 in Group 1 and 1.33 in group 2, consisting of 26 males (57.8%) and 19 females (42.2%) in group 1 and 20 males (57.1%) and 15 females (42.9%) in Group 2 ($p=0.95$). The first year seizure recurrence was 43.7%. The second seizure occurred within the first six months in 29 (83%) of the patients. Seizure recurrence occurred in 21 patients (60%) within the first three months, in 8 patients (22.9%) between four and six months, and in 6 patients (17.1%) between seven and twelve months after the first seizure. Comparison of the age at the first seizure, gender and characteristics of the first seizure in group 1 and 2 is shown in Table 1.

Table 1. Age at the first seizure, gender and characteristics of the seizure in Group 1 and Group 2

	Group 1 (n=45)	Group 2 (n=35)	p	OR (95 %CI)
	n (%)	n (%)		
Age at first seizure (mo.)	80.1 $\pm$ 52.8	85.2 $\pm$ 60.7	0.78	1
≥ 24 months	40 (88.9%)	27 (77.1%)	-	1.00
< 24 months	5 (11.1%)	8 (22.9%)	0.158	2.37 (0.7-8.02)
Gender				
Male	26 (57.8%)	20 (57.1%)	-	1.00
Female	19 (42.2%)	15 (42.9%)	0.955	1.03(0.42-2.51)
Seizure type				
Generalized	37 (82.2%)	25 (71.4%)	-	1.00
Focal	6 (13.3%)	4 (11.4%)	0.985	0.99 (0.25-3.86)
Combined	1 (2.2%)	3 (8.6%)	0.208	4.44(0.44-45.15)
Unidentified	1 (2.2%)	3 (8.6%)	0.208	4.44 (0.44-45.15)
Time of seizure				
Awake	26 (57.8%)	14 (40.0%)	-	1.00
At sleep	19 (42.2%)	21 (60.0%)	0.115	2.05 (0.84-5.04)
Seizure duration(min)				
< 5 min	10 (22.2%)	13 (37.1%)	-	1.00
5-20 min	31 (68.8%)	18 (51.5%)	0.213	0.51 (0.18-1.46)
> 20 min	4 (8.8%)	4 (11.4%)	0.909	0.91 (0.18-4.64)
Seizure recurrence in the first 24 hours				
No recurrence	38 (84.4%)	30 (85.7%)	-	1.00
Recurrence	7 (15.6%)	5 (14.3%)	0.875	0.90 (0.26-3.14)

OR: Odds ratio, CI: confidence interval, min: minute

Consanguinity, birth weight, normal or cesarean delivery, postnatal hospitalization, mental development, family history of epilepsy or febrile convulsion had no effect on seizure recurrence ($p>0.05$, $OR = 1$). There was no significant difference

in age, gender, seizure occurrence at sleep or at awake time, seizure type, duration, and recurrence of seizure in the first 24 hours ($p>0.05$). The most common seizure type in both groups was generalized seizures (82.2% and 71.4%), followed by focal

seizures in Group 1 and Group 2, 13.3% and 11.4%, respectively. Duration of the first seizure was similar in both groups, most lasting less than 20 minutes. The majority of seizures (84.4% and 85.7%) in both groups did not recur in the first 24 hours and the ratio of more than one seizure in the first 24 hours was similar in both groups, with 15.6% and 14.3% of seizures in Group 1 and Group 2, respectively ($p=0.875$). Combination of various parameters, being younger than 24 months at the first seizure, first seizure occurring at sleep, postnatal hospitalization and family history of epilepsy were investigated as risk factors of seizure recurrence, but there was not any significant difference between the groups ($p>0.05$). Cranial imaging was performed in 67 patients at the initial seizure, including cranial CT in 9 patients and MRI in 58 patients. Glial tumors were identified in two patients on MRI from Group 1 which required surgical intervention. Other pathologies were arachnoid cyst, neuroepithelial cyst, Chiari type 1 malformation, mesial temporal sclerosis, cystic encephalomalacia and hyperintensities in the occipital and parietal regions, enlargement of the subarachnoid space and other nonspecific findings in 12 patients, six patients from group 1 and six patients from Group 2. Abnormalities on MRI or CT were not significant for the recurrence of the seizure ($p=0.68$). Focal neurological signs on physical examination were observed in 3 patients which had no effect on recurrence of the seizure ($p=0.57$).

DISCUSSION

(ILAE) defines epilepsy, a disorder of the brain predisposing the patient to develop epileptic seizures, and there should be at least one seizure for the diagnosis of epilepsy (Fisher et al., 2014). In a child presenting with an unprovoked convulsion, we face some questions like: what caused the seizure?, will it recur? what expects my child in the future? Seizure recurrence risk is important for the child, family, and the doctors dealing with the child to take preventive measures at the appropriate time. Epilepsy develops in approximately 30% of children who experience afebrile seizures. The risk of epilepsy is approximately 20% lower if the child's development is appropriate for the age

and neurological examination, EEG, and cranial MRI findings are normal (Mohamad,2020). In a prospective study of 467 children who were followed after a first unprovoked seizure without antiepileptic treatment, 60% of children had seizure recurrence and most recurrences were in the first 2 years (Takami & Nakagawa,2021). In a meta-analysis regarding 815 children who presented with a first unprovoked seizure, seizure recurrence was reported ranging from 34.3% to 63.7% (Garcia Pierce et al., 2017). In our study, we observed seizure recurrence in 35 patients (44%) at the first year of the initial seizure, and most of the recurrence (83%) was in the 6 months, which was appropriate with the literature (Chen et al., 2024; Jiménez-Villegas et al., 2021; Takami & Nakagawa,2021). In some studies, seizures occurring at sleep were reported to have increased risk of recurrence (Berg & Shinnar,1991; Ramos Lizana et al., 2000; Shinnar et al., 1996). But, in our study, seizures at sleep or awake time did not have any impact on recurrence of the seizure. In the children who had cranial imaging for seizures, identifying a pathology requiring emergency medical or surgical intervention is 1% (Shinnar et al., 2001). In focal seizures and children with abnormal EEG, abnormal imaging findings are frequently reported (Berg et al., 2000). In our study, cranial MRI revealed some pathologies in 9% of the patients; two patients were diagnosed with glial tumors, underscoring the significance of cranial MRI for children with unprovoked seizures. Abnormal EEG, neuroimaging findings, nocturnal seizures, abnormal MRI, prior brain insult, and focal seizures were reported as significant factors for seizure recurrence in children (Berg,2008; Chen et al., 2024; Takami & Nakagawa,2021) Abnormal EEG was reported as the most significant factor for seizure recurrence (Berg, 2007; Chen et al., 2024; Debicki, 2017; Kanemura et al., 2015). In this study, we studied the population with normal EEG results, thereby excluding the influence of EEG abnormalities on seizure recurrence. However, we could not find any parameter which had any effect on the first-year seizure recurrence. The small size of the study population and the focus solely on the first-year seizure recurrence rate were limitations of our study.

Conclusion: Following a first unprovoked seizure, it is important to distinguish the patients with a high risk of seizure recurrence. We suggest that extended follow-up in larger series will be helpful to find the risk factors for seizure recurrence and detect epilepsy earlier in the pediatric population.

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