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Predictors of Intractability in Patients with Symptomatic Epilepsy

Tamer ÇELİK[1], Özlem HERGÜNER[2]

[1] Private Practice, Pediatric Neurology, Adana, Turkey
[2] Çukurova University Faculty of Medicine, Clinic of Pediatric Neurology, Adana, Turkey

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ABSTRACT

Objective: Childhood intractable epilepsy is a serious condition with catastrophic effects in neurodevelopment. Although there are numerous studies regarding which epileptic patients will develop intractable epilepsy, there is no clear data yet. In this study, it was aimed to investigate predictors affecting intractability in children with symptomatic epilepsy.

Material and Methods: In this study, we retrospectively reviewed data of 75 patients whose seizures still continue despite treatment with at least two antiepileptic drugs and who had been followed for at least one year in the Pediatric Neurology Clinic of Çukurova University Faculty of Medicine, Pediatric Neurology Department Hospital and investigated risk factors determining intractability in childhood epilepsy by dividing the patients into three groups. Group 1 included patients who had at least one seizure in the last six months despite taking at least two antiepileptic drugs, Group 2 included patients who had less than one seizure in the last six months despite taking at least two antiepileptic drugs, and Group 3 included patients with symptomatic epilepsy, who used at least two antiepileptic drugs in proper dosages and did not have any seizures for the past one year.

Results: While the most important risk factor in intractable epilepsy development was found as status epilepticus (SE) ($p< 0.05$), the age of onset of seizures, presence of mental retardation, presence of a neurologic abnormality, epileptic activity in EEG and presence of neuroradiologic abnormality, consanguinity, epilepsy history in the family, presence of neonatal seizure, febrile convulsion, and seizure incidence before starting drugs were not found to be significant ($p> 0.05$).

Conclusion: In this study, it was concluded that history of status epilepticus was an important and independent risk factor for intractable epilepsy development. During medical follow-up of epileptic patients and patients with risk factors, it is required to start rational drug use early and apply necessary interventions before the patients before the status at the onset of seizure.

Keywords: Epilepsy, intractable factors

ÖZ

Semptomatik Epilepsili Hastalarda Dirençliliği Belirleyen Faktörler

Giriş: Çocukluk çağı dirençli epilepsileri, nörogelişimde katastrofik etkileri olan ciddi bir durumdur. Hangi epileptik hastaların dirençli epilepsi geliştireceği ile alakalı pekçok çalışma olsa da, bu konuda net bir veri yoktur. Bu çalışmada semptomatik epilepsili çocuk hastalarda dirençliliği belirleyen faktörleri araştırdık.

Gereç ve Yöntemler: Bu çalışma, Çukurova Üniversitesi Tıp Fakültesi Çocuk Nöroloji Polikliniği'nde izlenen ve son bir yıl içinde poliklinik takibi yapılan, en az iki antiepileptik ilaçla tedavi edilmesine rağmen nöbetleri devam eden 75 hastanın verileri retrospektif olarak değerlendirilip gruplara ayırarak çocukluk çağı epilepsilerinde dirençli olmayı belirleyen risk faktörlerini araştırdık. Grup 1'de, en az iki antiepileptik ilaç almasına rağmen son altı ayda ortalama ayda en az bir nöbeti olanlar; Grup 2'de, en az iki antiepileptik almasına rağmen son altı ayda ayda birden az nöbeti olanlar; Grup 3'te ise, semptomatik epilepsiye sahip olan, en az iki antiepileptik ilacı yeterli dozda kullanan ve en az bir yıldır nöbetsiz olanlar olarak tanımlandı.

Bulgular: Dirençli epilepsi gelişiminde en önemli risk faktörü status epileptikus (SE) olarak bulunurken ($p< 0.05$), nöbet başlangıç yaşı, mental retardasyon varlığı, nörolojik anormallik varlığı, EEG'de epileptik aktivite ve, nöroradyolojik anormalliğin varlığı, akrabalık, ailede epilepsi öyküsü, yenidoğan nöbeti varlığı, febril konvülziyon, ilaç başlamadan önceki nöbet sıklığı anlamlı olarak bulunmadı ($p> 0.05$).

Sonuç: Bu çalışmada status epileptikus öyküsünün dirençli epilepsi gelişimi için önemli ve bağımsız bir risk faktörü olduğu sonucuna vardık. Epileptik ve risk faktörü taşıyan hastaların medikal izleminde akılcı ilaç kullanımı için daha erken davranılması, hastalar nöbet başlangıcında statusa girmeden gerekli müdahalelerin yapılması gerekmektedir.

Anahtar Kelimeler: Epilepsi, direnç faktörleri

Corresponding Address

Tamer ÇELİK

Private Practice, Pediatric Neurology, ADANA-TURKEY
e-mail: tamercelik33@gmail.com

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INTRODUCTION

Epilepsy is a troubling disease treatment-wise in the childhood period, and childhood intractability epilepsy is a serious condition with catastrophic effects in neurodevelopment. Knowing prognosis in patients with epilepsy is highly vital in terms of onset of treatment, its continuance, and termination. Patients with epilepsy whose seizures do not respond to antiepileptic drugs successfully are accepted as intractable epilepsy. This condition is also referred to as refractory epilepsy, drug-resistant or pharmacoresistant epilepsy (1). According to the definition of Task Force of the International League Against Epilepsy (ILAE), drug-resistant epilepsy is failure to achieve seizure freedom by two tolerated and appropriately chosen and used antiepileptic drugs (monotherapi or combined) (2).

Despite lack of a standard definition of treatment resistance, the widely accepted definition is as follows: the continuance of seizures in the frequency of one or more than one seizure a month although at least two appropriately chosen antiepileptic drugs are used at the maximum tolerated dosages. It is possible that 20-40% of patients with epilepsy (approximately 400.000 people living in the USA) suffer from intractable epilepsy. In a collected work evaluating 35 studies, prevalence and incidence rates have been reported as 0.30 and 0.15, respectively (3). According to research conducted in 1995, annual cost for epileptic patients in the US was 12.5 billion dollars, and drug-resistant epilepsy made up a significant proportion of this cost (4,5).

In detecting the prognosis early and correctly, the cases must be followed with frequent intervals and their neurologic and psychomotor developments must be evaluated. There are many studies emphasizing that knowing in whom prognosis is good and poor beforehand enables the start of alternative treatment methods early particularly in patients with poor prognosis. There is not total compatibility between the outcomes regarding predictive factor affecting both seizure, developmental and psychiatric prognoses (6,7).

In this study, it was aimed to determine possible factors affecting intractability in cases with no underlying neurological diseases and followed with the diagnosis of intractable epilepsy.

MATERIALS and METHODS

We retrospectively reviewed data of 75 patients whose seizures still continue despite treatment with at least two antiepileptic drugs and who had been followed for at least one year in Çukurova University Faculty of Medicine, Pediatric Neurology Department Hospital and investigated risk factors determining intractability in childhood epilepsy by dividing the patients into three groups. Ethics board approval was obtained for the study. Systemic and neurological examinations were done, and intelligence evaluations (with Stanford-Binet or WISC-R) and laboratory tests (cerebral computed tomography or MRI, metabolic scans, and etc.) oriented ate seizure etiology were performed. The patients were divided into three groups. Group 1 included patients who had at least one seizure in the last six months despite taking at least two antiepileptic drugs, Group 2 included patients who had less than one seizure in the last six months despite taking at least two antiepileptic drugs, and Group 3 included patients with symptomatic epilepsy, who used at least two antiepileptic drugs in proper dosages and did not have any seizures for the past one year. Exclusion criteria included the following: idiopathic epilepsy, neurodegenerative disease, neurometabolic disease, febrile convulsion, West syndrome, and Lennox-Gestaut syndrome. Neurologic abnormalities were considered as the presence of abnormalities detected on physical examination of the patient (hemiparesis, strabismus, microcephalia, and etc.).

All patients had at least two interictal EEGs during follow-up. If one of them was abnormal, then EEG was accepted abnormal. Presence of mental retardation was accepted as a score of 70 and under in the intelligence score. Status epilepticus was defined as history of seizure lasting more than 30 minutes without betterment in consciousness. Presence of lesion on the MRI was recorded by identifying in accordance with localization and nature of the leisure (migration anomaly, glottic lesion, ventricle dilatation, and such findings were evaluated as pathological).

Statistical Analysis

SPSS 18.0 package program was used in the analysis of data. Categorical variables were expressed as number and percentage, and numerical variables were expressed as mean and standard deviation (median and minimum-maximum, where necessary). Chi-square test was used for group comparisons of categorical estimates. Kruskal Wallis test was used for group comparisons of numerical estimates without normal distribution. Binary sub-group comparisons for conditions with difference were made with Mann-Whitney U test with Bonferroni correction. Logistic regression analysis was performed to determine the estimates considered to have affected the results of intractability development in epilepsy. Odds ratio and 95% confidence interval was determined. Statistical significance in all tests was set at 0.05.

RESULTS

Demographic Data

Mean age of the 75 patients included into this study was 23.925 ± 43.286 months (min-max= 1-168 months), and 32 were girls and 43 were boys. There were 43 patients (57%)

Table 1. Demographic data of the groups

	Group 1	Group 2	Group 3	p
Age (month) mean + SD	11.66 + 24.71	17.93 + 35.15	98.50 + 57.71	>0.05
(min-max)	3-168	1-156	4-168	
Sex n (%)				
Boy	23 (% 53)	15 (% 62)	5 (% 55)	>0.05
Girl	20 (% 47)	9 (% 38)	4 (% 45)	
Mental retardation				
Present	39 (91)	19 (83)	9(100)	0.32
Absent	4 (9)	4 (17)	0 (0)	
Neurological abnormality				
Present	26 (61)	19 (83)	5 (56)	0.14
Absent	17 (39)	4 (17)	4 (44)	
Consanguinity between the parents				
Present	23 (54)	10 (44)	6 (67)	0.47
Absent	20 (46)	13 (56)	3 (33)	

Table 2. Presence of anomalies on ENMG and MRI

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	p
ENMG anomaly				
Present	38 (88)	23 (100)	9 (100)	0.13
Absent	5 (12)	0 (0)	0 (0)	
MRI anomaly				
Present	34 (79)	18 (78)	6 (67)	0.71
Absent	9 (21)	5 (22)	3 (33)	

ENMG: Electroneuromyography, MRI: Magnetic resonance imaging.

in Group 1 (refractory group), 23 patients (31%) in Group 2 (non-refractory group), and nine patients (12%) in Group 3 (seizure-free for one year). Mean ages of the patients in Group 1, 2 and 3 were found respectively as 11.66 ± 24.71 months (min-max= 3-168 months), 17.93 ± 35.15 months (min-max= 1-156 months), and 98.50 ± 57.71 months (min-max= 4-168 months). No difference was detected between the groups in terms of sex and age (p> 0.05) (Table 1). A statistically significant difference was not detected between the groups when they were divided into groups according to their mental retardation, neurological abnormality and consanguinity statuses (p> 0.05) (Table 1). When the patients were evaluated in terms of having or not having epileptic activity on interictal ENMG and presence of an anomaly on MRI, a statistically significant difference was not detected between the groups (p> 0.05) (Table 2).

Seizure Characteristics of the Patients

There was no statistically significant difference when the patients were divided whether they had a family history of epilepsy, neonatal epilepsy history or previous febrile convulsion history or not (p> 0.05) (Table 3). Statistically significant difference was detected between the groups when divided regarding history of status epilepticus (p= 0.005) (Table 3). On logistic regression analysis, the presence of status epilepticus increased the risk of intractable epilepsy development by 15.840-folds (95% CI= 1.952-128.526).

Seizure frequency of the patients before the drugs was questioned. Seizure frequency was divided into as only one seizure, status epilepticus, cluster seizure, and more than two seizures. In Group 1, 14 patients (33%) only had one seizure, two patients (4%) had status epilepticus, four patients (9%) had cluster seizure, and 23 patients (54%) had more than two seizures. In Group 2, 12 (52%) patients only had one seizure and 11 (48%) patients had more than two seizures. In Group 3, two patients (22%) only had one seizure and seven patients (78%) had more than two seizures. A statistically significant difference was not detected between the groups in terms of seizure frequency before the drugs (p> 0.05) (Table 4).

Table 3. Distributions between the groups regarding seizure characterists

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	p
Epilepsy history of family				
Present	16 (37)	5 (22)	5 (56)	0.16
Absent	27 (63)	18 (78)	4 (44)	
Status epilepticus				
Present	18 (42)	1 (4)	2 (22)	**0.005**
Absent	25 (58)	22 (96)	7 (78)	
History of neonatal seizure				
Present	12 (28)	9 (39)	2 (22)	0.54
Absent	31 (72)	14 (61)	7 (78)	
History of febrile convulsion				
Present	18 (42)	5 (22),	1 (11)	0.089
Absent	25 (58)	18 (78)	8 (89)	

Table 4. Frequency of seizures before the start of drugs between the groups

Frequency of seizures before the start of drugs	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	p
Only one seizure	14 (33)	12 (52)	2 (22)	
Status epilepticus	2 (4)	0 (0)	0 (0)	
Cluster seizure	4 (9)	0 (0)	0 (0)	0.366
More than two seizures	23 (54)	11 (48)	7 (78)	
Total	43 (100)	23 (100)	9 (100)	

DISCUSSION

In this retrospective study in which we investigated factors for intractable epilepsy, the most important risk factor was found as status epilepticus; however, the age of onset of seizures, presence of mental retardation, presence of a neurologic abnormality, epileptic activity in EEG and presence of neuroradiologic abnormality, kinship, epilepsy history in the family, presence of neonatal seizure, febrile convulsion, and seizure incidence before starting drugs were not found to be significant. With proper and sufficient treatment, remission can be achieved in 60-70% of childhood epilepsy cases, and antiepileptic drug use can be terminated in approximately 50% (8-11). Intractable epilepsy rate has been found as 10% in a study by Berg and colleagues (12).

Risk factors have been tried to be evaluated in many studies. However, the design of these studies differs (11). A single factor has not been found as a predictor. Two or more factors have been found beneficial to detect cases that do not respond to drug treatment (12,13). Prospective studies on the matter are limited. Therefore, it is not easy to understand the differences between the studies. However, the main three components used in every definition are non-responsiveness to antiepileptic drugs, seizure frequency, and timing. While there is consensus on the first two components, the concept of time shows difference between the studies (13).

In our study, we determined six months as the time needed to evaluate resistance to treatment. Ramos-Lizana et al. and Oskoui et al. have accepted this time frame as 12 months (16,17). As a result, there are differences between the rate of intractable epilepsy and the risk factors determined due to definition of intractability, study design, and study groups. The most important determinant in intractable epilepsy in most studies have been found as response to the first antiepileptic treatment given (11,18-21).

While more than half of the patients respond to the first antiepileptic treatment, it is possible that less than 20% respond to subsequent drug trials. The risk of intractable epilepsy increases with each unsuccessful antiepileptic treatment trial. Studies have shown that underlying etiology and reason for seizures are also determinants. Some pediatric epilepsy syndromes are almost completely intractable. In the literature, status epilepticus has also been presented as a factor determining intractable epilepsy (22-24).

In all studies, children with symptomatic epilepsy have been found to carry higher risk for intractable epilepsy. In our study, all of our patients were children with symptomatic epilepsy. There is no similar study in the literature in this regard, and status epilepticus was found as the most important risk factor. In the studies by Ramos and Casetta et al., status epilepticus has not been found as a risk factor (16,25). This result, which is contrary to our results, is due to the difference between study groups. While symptomatic patients made up just a part of the patients in the groups of Ramos and Casetta, all of our patients were symptomatic. However, there are also numerous studies that have reported status epilepticus as the most important risk factor for intractable epilepsy (26-28). These conflicting results bring to mind the question if SE is the cause or outcome. Status epilepticus can be considered a cause in prognosis not just an outcome if it is considered that excitatory amino acids have a neurotoxic effect during prolonged seizures and lead to neuron loss, and thus deteriorate the excitatory and inhibitory balance between the neurons (28).

Presence of mental retardation on diagnosis was not found as a risk factor in our study. In the literature, there are several studies reporting that global developmental retardation is a factor of poor prognosis (16,29). This difference is due to the characteristic of our study population. Since case and control groups had a symptomatic etiology homogeneously, MRI presence did not create any significant difference between the groups. In our study, presence of neurological anomaly on diagnosis was not found as a risk factor in our study. There are several studies reporting otherwise in the literature (16,27,29). In the study by Ramos-Lizana, a statistically significant relation has not been found between neurological anomaly on diagnosis and development of intractability (16). We believe that this difference is based on the difference between study methods.

Presence of epileptic anomaly on EEG was not found as a risk factor in our study. EEG results have not been taken into consideration in all of the pioneering studies conducted on this subject (30).

A couple of studies have investigated EEG and its relation to prognosis. Shafer et al. have concluded that lack of generalized epileptiform activity on initial EEG is a good prognostic factor but other EEG anomalies are not related to prognosis (31).

In a retrospective study by Ko et al., the relation between EEG anomalies and intractability development has been scrutinized and only diffuse retardation and presence of focal sharp waves activity have been found as independent risk factors; however, since the study had handicaps, it did not receive general acceptance (29). A relation could not be found between EEG anomalies and development of intractable epilepsy in studies by Ramos-Lizana and Altunbaşak et al. (16,32). In our study, we concluded that the presence of neuroradiological anomalies was not a risk factor in terms of intractable epilepsy development. There are many studies reporting otherwise (13).

It was seen that in all of these studies, symptomatic and idiopathic/cryptogenic patients have been evaluated together and naturally MRI anomalies have been found significantly related to intractability development. We believe that the difference in our patient population caused the result which is incompatible with the literature.

Blood relation/kinship between the mother and father was not found a risk factor regarding intractable epilepsy development. Altunbaşak et al. have also questioned blood relation/kinship between the parents, and it has not been found as a significant factor for intractable epilepsy development (32). In our study, the presence of familial epilepsy history was not found a risk factor. Many studies in the literature support our finding (29,30).

Presence of neonatal seizure was not found as a risk factor in our study. There are studies reporting otherwise in the literature (28). Ramos-Lizana could not find a statistically significant relation between neonatal seizure and development of intractable epilepsy in their study (16). We believe that these different results depend on the methodology behind the studies and patient selection criteria.

Presence of febrile convulsion was not found as a risk factor in our study. When the literature was scanned, we observed that many studies have come to the same conclusion (30). Seizure frequency before starting the drugs was not found as a risk factor for intractable epilepsy development in our study. Similarly, this parameter has not been found as a risk factor in the study by (17).

To conclude, we found that previous status epilepticus was a significant and independent risk factor for the development of intractable epilepsy. We can say that clinicians must ac faster in using rational multiple drugs in the medical follow-up of these patients. Moreover, it is of utmost importance to perform necessary intervention before the patients go into status at the onset of their seizures.

Ethics Committee Approval: This study was approved by the Çukurova University Faculty of Medicine Research Ethics Committee (Decision no: 10, Date: 23.12.2010).

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