Risk Factors for Seizure Recurrence in Epileptic Children after Withdrawal of Antiepileptic Drugs

Epilepsili Çocuklarda Antiepileptik İlaçların Kesilmesinden sonra Nöbet Tekrarı için Risk Faktörleri

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Objectives: In epileptic children, the risk of seizure recurrence after antiepileptic drug (AED) withdrawal varies from 8% to 40%. In this study, we investigated the rate and predictive factors of seizure recurrences after AED discontinuation.

Patients and Methods: Children who were treated with AEDs for 2 to 6 years were evaluated after 1.2 to 13 years following discontinuation of treatment. A total of 88 children (41 girls, 47 boys) were evaluable.

Results: Recurrent seizures were encountered in 19 patients (21.5%). Seizure recurrence occurred during the first year following drug withdrawal in 17 patients (89%). Factors associated with an increased risk of seizure recurrence were as follows: the presence of mental retardation, abnormal neurologic findings, partial seizures, and more than 10 epileptic seizures, appearance of epileptic foci on EEG recordings before the discontinuation of medication, and withdrawal of drugs after 10 years of age ($p<0.05$).

Conclusion: Children who do not exhibit the above-mentioned risk factors seem to have an excellent chance of remaining seizure-free after withdrawal of AEDs.

Key Words: Anticonvulsants; child; electroencephalography; epilepsy/complications/drug therapy; prognosis; recurrence; risk factors; substance withdrawal syndrome.

Amaç: Epileptik çocuklarda antiepileptik ilaçların kesilmesinden sonra nöbet tekrarlama oranı % 8-40 arasında değişmektedir. Bu çalışmada antiepileptik ilaç kesilmesinden sonra nöbet rekürens oranı ve buna etkili olabilecek prediktif faktörler araştırıldı.

Hastalar ve Yöntemler: Antiepileptik ilaçla 2-6 yıl arasında değişen süreyle tedavi edilen çocuklar tedavilerinin kesilmesinden 1.2-13 yıl sonra değerlendirildi. Takipte epilepsili 88 çocuğa (41 kız, 47 erkek) ulaşıldı.

Bulgular: On dokuz olguda (%21.5) nöbetlerin tekrarladığı gözlendi. Bunların 17'sinde (%89) nöbet tekrarı tedavi kesilmesini izleyen ilk yıl içinde meydana geldi. Hastalarda mental retardasyon veya anormal nörolojik bulguların olması, parsiyel nöbet geçirme, toplam nöbet sayısının 10'un üzerinde olması, ilaç kesilmesinden önce çekilen EEG'lerde epileptik odak varlığı, ilaçların 10 yaşından sonra kesilmesi nöbet tekrarı açısından istatistiksel olarak anlamlı risk faktörleri olarak belirlendi ($p<0.05$).

Sonuç: Belirtilen risk faktörlerine sahip olmayan çocuklarda, ilaçla tedavinin kesilmesinden sonra nöbetsiz kalma olasılığının oldukça yüksek olduğu sonucuna varıldı.

Anahtar Sözcükler: Antikonvulzanlar; çocuk; elektroensefalografi; epilepsi/komplikasyon/ilaç tedavisi; prognoz; rekürens; risk faktörleri; ilaç kesilmesi.

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In epileptic children, the risk for seizure recurrence following withdrawal of antiepileptic drugs (AEDs) ranges from 8% to 40%.[1] Some predictive factors have been proposed for recurrences including age at the onset of seizure, the type of seizure, the duration of illness, the history of status epilepticus, mental and neurological status, and EEG findings.[2-5] In this study, the predictive factors and the rate of seizure recurrence after discontinuation of AEDs were retrospectively evaluated in epileptic children.

PATIENTS AND METHODS

The study included 88 epileptic children (41 girls, 47 boys) who received treatment with AEDs. The indication for AED treatment was the occurrence of at least two afebrile convulsions. Those with febrile convulsions, metabolic or degenerative central nervous system disorders, and neonatal convulsions were not included. Seizure types were classified according to the revised classification of the International League Against Epilepsy in 1989.[6] Treatment with AEDs was administered for 2 to 6 years (3.53±1.75 years) and was tapered within 4 to 6 months before discontinuation. All patients were available for follow-up for a mean period of 3.23±1.9 years (range 1.2 to 13 years). Occurrence of any convulsions after AED withdrawal was investigated by a questionnaire sent to the parents, and any positive responses were further inquired by direct contact with the parents. Thus, incidence of seizure recurrence was calculated. In addition, risk factors for recurrence were determined by comparison of the findings from the patients with or without recurrent seizures.

Statistical analyses were made with the use of the Fisher's exact and chi-square tests and a *p* value of less than 0.05 was regarded as significant.

RESULTS

The age of seizure onset varied from 0.25 to 13 years (mean 3.87±3.88 years). Sixteen patients had partial seizures and 72 patients had generalized seizures.

Of the study group, 82 patients received monotherapy including phenobarbital (n=47), carbamazepine (n=21), valproate (n=9), and phenytoin (n=5). The remaining six patients were administered polytherapy. The duration of treatment varied from two to eight years (mean 3.53±1.75 years). The number of seizures that occurred before and during treatment ranged from 2 to 50 (mean 6.3±9.7 seizures). Antiepileptic drugs were tapered off within 4 to 6 months following a seizure-free period of 2 to 6 years (mean 2.76±0.31 years). Evaluation of seizure recurrence was made after 1.2 to 13 years (mean 3.23±1.9 years) following withdrawal of AEDs.

The overall recurrence rate following withdrawal of AEDs was 21.5% (n=19). Fifteen patients (79%) experienced seizures within the first six months, while two patients (11%) had seizures within 6 to 12 months. Two patients had recurrent seizures after 1 to 5 years (5%), and above 5 years (5%) of withdrawal, respectively. Of the recurrent seizures, 11 were generalized and eight were partial. The patients with partial seizures had significantly higher risk for recurrence when compared to those with generalized seizures (8/16 vs 11/72 patients) ($p<0.05$) (Table 1).

The presence of abnormal neurologic findings and mental retardation differed significantly between patients with and without seizure recurrence ($p<0.05$). Recurrent seizures were associated with abnormal neurologic findings in six patients (32%), which included spastic hemiparesis (n=5) and spastic diparesis (n=1). In contrast, only two patients (3%) without seizure recurrence had mild hemiparesis. On the other hand, mental retardation was documented in eight (44%) and six patients (9%) with and without seizure recurrence, respectively (Table 1).

Before discontinuation of AEDs, abnormal EEG findings were found in 31 patients including epileptic focus (n=6), subcortical epileptiform discharges (n=4), and paroxysmal slow wave activity (n=21). There was a significant difference between the patients with and without seizure recurrence with respect to abnormal EEG findings (10/19, 63% vs 21/69, 30%).

Computed brain tomography and/or cranial magnetic resonance imaging were obtained in 49 patients. Seven patients in the recurrence group exhibited abnormal findings including cortical atrophy (n=2), cortical atrophy and gliotic changes (n=3), white matter

involvement with partial callosal agenesis (n=1), and cerebral hemiatrophy (n=1), whereas only two patients had cortical atrophy in the seizure-free group (p<0.05).

Having more than 10 seizures before and during treatment and withdrawal of antiepileptic drugs after 10 years of age were found as significant risk factors for recurrence (p<0.05) (Table 1).

TABLE 1

Risk factors for seizure recurrence

	Recurrence (n=19)		Recurrence-free (n=69)		p
	n	(%)	n	(%)	
Birth asphyxia	5	26.5	7	10	>0.05
Family history of febrile convulsion	1	5	11	16	>0.05
Family history of epilepsy	3	16	8	12	>0.05
Mental retardation	8	43	4	6	**<0.05**
Abnormal neurologic findings	6	32	2	3	**<0.05**
Age at seizure onset (year)					
< 2	8	42	37	54	
2-5	3	16	11	16	
> 5	8	42	21	30	>0.05
Seizure type					
Partial	8	43	8	12	
Generalized	11	57	61	88	**<0.05**
EEG before treatment					
Normal	2	10.5	9	13	
Paroxysmal activity	5	26.5	17	25	
Epileptic focus	9	47	27	39	
Subcortical epileptic discharges	3	16	16	23	>0.05
EEG before discontinuation of AEDs					
Normal	9	47	48	69	
Paroxysmal activity	5	26.5	16	23	
Epileptic focus	5	26.5	1	2	
Subcortical epileptic discharges	–		4	6	**<0.05**
Abnormal neuroradiologic findings[#]	7		2		**<0.05**
Duration of treatment (year)					
<3	13	68	35	51	
3-5	1	6	19	27	
>5	5	26	15	22	>0.05
Seizure-free period (year) before discontinuation of AEDs					
<3	17	89	42	61	
3- 5	1	5.5	16	23	
>5	1	5.5	11	16	>0.05
Number of total seizures					
2< 5	13	68	55	80	
6-10	2	11	13	19	
>10	4	21	1	1	**<0.05**
Age at the withdrawal of AEDs (year)					
< 5	2	11	19	28	
5-10	3	16	29	42	
>10	14	73	21	30	**<0.05**

99 patients had neuroradiologic imaging

In nearly half of our patients (45/88, 51%), seizures began below two years of age. There was no difference between the patients with and without seizure recurrence in respect to the age of seizure onset. Similarly, birth asphyxia, a history of febrile or afebrile convulsions in family members, age during the first seizure, EEG findings at the beginning of the treatment, duration of treatment, and seizure-free period before withdrawal of AEDs were not found as significant risk factors for recurrence (p>0.05).

DISCUSSION

The discontinuation of AEDs after an acceptable seizure-free period is desirable, but some patients might have recurrent seizures during or after withdrawal period. Therefore, clinicians must be aware of the risk factors for recurrence and inform the parents before discontinuation of drugs.

Of eighty-eight patients whose treatment with AEDs was discontinued after at least two seizure-free years, seizures recurred in 21.5%. Several studies conducted in pediatric epileptic patients have reported a recurrence rate ranging between 8% and 40%.[1] Seizure recurrence is encountered especially during the first year following the discontinuation of AEDs.[2] In our study, 90% of the recurrences fell within the first year. Relevant data of published series of pediatric epileptic patients concerning seizure recurrence and risk factors after discontinuation of AEDs are summarized in Table 2.[2,7-13]

It has been proposed that the presence of an organic cerebral etiology (such as birth asphyx-

TABLE 2

Recurrence rates and risk factors reported in the literature

References	2	6	7	8	9	10	11	12	Our study
Number of patients	148	425	146	68	116	433	191	70	88
Seizure-free time (year)	4	>2	>2	4	>2	1-4	>2	>2	>2
Follow-up (year)	18.6	8	4.3	2.7	4.3	5-6	>2	1.5	3.23
Recurrence rate (%)	28	11.8	25	26	22	36	22.5	28.5	21.5
Time of recurrence (%)									
1st year	56	62		79	High	86	79	75	90
2nd year	68		75				93		
5th year	85								95
Risk factors for recurrence									
Birth asphyxia		–							–
Mental retardation		+		+				+	+
Abnormal neurologic findings	+	+	–	+	–	+		+	+
Abnormal neuroradiologic findings									+
Positive family history of epilepsy	–	–	–	–	–	–			–
Partial seizures	+	+	–	–	–	+			+
Different seizure types	+	–	–	–	–	+		+	–
EEG findings		–	+	+	–	+	+	+	+
Pretreatment seizure frequency		+	–		–			+	
Number of seizures after AEDs	–	–	–	+	–				
Number of total seizures									+
Early onset seizures	–	–	–	+	–	–	–		–
Late onset seizures	–	–	–	–	+	–	+		–
Age at AED withdrawal	–	–	–	–		–			+
Duration of seizure-free period		–				+	+		–
Duration of therapy									–

[2]Thurston et al.; [7]Matricardi et al.; [8]Arts et al.; [9]Emerson et al.; [10]Bouma et al.; [11]Todt; [12]Mastropaolo et al.; [13]Gherpelli et al.

ia) and/or abnormal neurologic findings such as mental retardation result in increased seizure recurrence.[2,7,9,11,13] However, this relationship has not been confirmed by several studies.[3,5,8,10] In our study, the presence of birth asphyxia was not correlated with seizure recurrence; however, mental retardation and neurologic deficits were found as significant predictive factors for recurrence. The recurrence rate was also higher in patients with abnormal neuroradiologic findings ($p<0.05$); of nine patients with pathological findings, seven patients (77%) developed recurrent seizures.

The type of seizures, in particular partial seizures,[2,7,11] and both generalized and focal seizures and symptomatic epilepsy[2,8,11,13] have been demonstrated as significant predictive factors for seizure recurrence. According to some reports, however, seizure type is not a significant factor.[5,8-10,12] In our study, patients with partial seizures exhibited a significantly increased risk for recurrence ($p<0.05$).

Our study also showed that abnormal EEG findings obtained before discontinuation of AEDs were significantly associated with seizure recurrence. Similar observations have been reported in some studies.[7,9,11-13]

Although the number of seizures before treatment has been shown as a significant predictive factor for recurrence in one study,[7] this has not been the case in several others.[8,10,12] Similarly, there are conflicting reports on the role of the number of seizures during treatment.[2,7-10,12] Gherpelli et al.[13] have reported that more than 10 seizures experienced before seizure control impose a significant risk on recurrence. In our study, having more than 10 seizures during pretreatment and treatment periods was found as a significant predictive factor for seizure recurrence ($p<0.05$).

Emerson et al.[9] have stated that early onset of seizures is a risk factor for seizure recurrence. It has also been reported that patients with a late onset of epilepsy are at a higher risk for recurrence.[5,10,12,14] There are studies, however, in which no association has been shown between age of onset of seizures and seizure recurrence.[2,7,8,11,13] We could not find any correlation between the age of onset of seizures and seizure recurrence ($p>0.05$).

According to several studies, age at the time of discontinuation of AEDs is not an important factor for recurrence.[2,7-9,11,12] However, our findings showed that epileptic children whose treatment was discontinued after 10 years of age exhibited an increased recurrence rate ($p<0.05$).

The significance of the length of seizure-free period before the discontinuation of AEDs is controversial.[11,12,15] In several studies, similar recurrence rates have been reported ranging from 26% to 28% and 22% to 25% following a seizure-free period of more than four years and two years, respectively.[2,7,8,10,16] In our study, the recurrence rate was 21.5% after a seizure-free period of more than two years and we did not find any correlations between the length of seizure-free periods and the recurrence rate ($p>0.05$).

In many studies, no association has been observed between a family history of epilepsy and the risk for recurrence.[2,7-12] Our results were similar to these observations.

A wide range of recurrence rates reported between 8% and 40% and controversy on predictive risk factors may be explained by diverse study populations, prospective versus retrospective analyses, different types of epilepsy and its causes, duration of therapy, and varying follow-up periods after discontinuation of treatment.

It is obvious that development of seizures after discontinuation of treatment is undesirable both for patients and physicians, but nearly one-fifth of epileptic patients face recurrent seizures. In spite of the presence of many studies suggesting some predictive factors for recurrence, definite criteria have not been established. Nevertheless, the parameters recommended to predict recurrences should be evaluated in each patient. Adequate information should be given to the patients and their parents concerning the risks for recurrences and all patients should be carefully observed especially during the first year of discontinuation of AEDs.

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