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Risk of recurrence after drug withdrawal in childhood epilepsy

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ABSTRACT

Objectives: After a reasonable seizure-free period, discontinuation of antiepileptic drugs (AED) is usually decided in epileptic patients despite the risk of seizure recurrence. In children, risk of recurrence after discontinuation of AED is generally 20–40%; however, there is still no general agreement on the criteria to predict safe discontinuation. This study was designed to determine the risk of recurrence and related risk factors after drug withdrawal in epileptic children.

Methods: 200 epileptic patients between 1 month and 15 years of age who were followed at least 1 year after drug withdrawal at a child neurology center between January 1993 and December 2005 formed the study population of this retrospective study. Patients were classified into groups according to defined risk factors for recurrence.

Results: Of 200 patients (118 boys, 82 girls), overall recurrence rate was 27%. Girls were more likely to have a seizure recurrence than boys, with the difference approaching statistical significance ($p = 0.058$). EEG recordings after withdrawal (post-withdrawal EEG) in the follow-up were significantly different in the patients with recurrence with respect to presence of an abnormality ($p = 0.05$). In the multivariate Cox regression analysis, female gender and abnormal post-withdrawal EEG were the risk factors influencing seizure recurrence, with female gender identified as the main risk factor.

Conclusions: Although the decision to discontinue AED treatment necessitates evaluation of each patient individually, our study suggests that female patients and those with abnormal EEG after withdrawal require more cautious follow-up because of the high risk of recurrence.

1. Introduction

In patients with epilepsy, the critical question of discontinuation of antiepileptic drugs (AED) arises after a seizure-free period. Most children will remain seizure-free after drug withdrawal since risk of recurrence after discontinuation of AED is generally 20–40% in children.[1–5] Age at onset of seizures, idiopathic etiology without a neurological disease, absence of interictal abnormalities on first electroencephalogram (EEG) and EEG before withdrawal, duration of AED withdrawal and seizure-free period before withdrawal are associated with a low risk of recurrence; however, there is still no general agreement with respect to the criteria to predict safe discontinuation.[1–7]

In view of the long-term adverse effects of AED together with the psychosocial and economical burden of epilepsy, it is necessary to determine the prognostic factors for drug withdrawal with lower risk of recurrence.

This study was designed to determine the risk of recurrence and related risk factors after drug withdrawal in children with epilepsy diagnosed and treated in a child neurology center during a long time period.

2. Patients and methods

Epileptic patients whose AED were withdrawn and who were followed at least 1 year after withdrawal between January 1993 and December 2005 in the outpatient clinic of the Department of Pediatric Neurology, Hacettepe University, were included in the study. Inclusion criteria were as follows: (1) Age at first seizure between 1 month and 15 years, (2) follow-up period of at least 1 year after the withdrawal, (3) seizures not due to neurometabolic or infectious diseases of the central nervous system (CNS), and (4) no history of seizures in the newborn period. Patients with a

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Abbreviations: AED, antiepileptic drug; EEG, electroencephalogram; MRI, magnetic resonance imaging.

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history of single seizures were not excluded if they fulfilled the criteria of epilepsy with regard to their clinical ictal symptoms and epileptic discharges on EEG. A total of 200 patients (118 boys, 82 girls) were included in the study. After retrospective collection of clinical and medical data from the hospital's medical records, patients were interviewed by telephone in December 2006 to determine if seizures recurred in the long-term follow-up (133 patients). Patients were sent letters if they could not be reached by telephone. Information in the medical records of the patients was used for the analysis if they could not be reached by telephone or letters (58 patients). Mean duration of follow-up in overall group was 39.9 ± 38.2 (0.25–172 months). Maximum duration of follow-up was 172 months (14 years and 4 months) after AED withdrawal. The mean age at onset of first seizure was 6.3 ± 3.8 years (min: 0.1 months, max: 15 years).

Seizures were classified according to the 1989 classification of the International League Against Epilepsy (ILAE).[8] Patients with underlying signs and symptoms of brain injury, delayed psychomotor development, neurological abnormalities and abnormal neuroimaging studies were defined as having symptomatic epilepsy; those with normal physical and neurological examination and normal neuroimaging studies were regarded as having idiopathic epilepsy; and those not belonging to either idiopathic or symptomatic epilepsy groups were regarded as having cryptogenic epilepsy. Mental retardation was generally estimated based on the neurological examination and clinical estimation; however, neuropsychological tests were also applied when mental retardation was suspected. Of the total, 18 patients had mental retardation. Magnetic resonance imaging (MRI) studies were available in 149 patients, 114 of which were normal. Abnormal MRI consisted of asymmetrical ventricular dilatation, mesial temporal lobe sclerosis, cortical dysplasias, periventricular leukomalacia, atrophies due to perinatal injury or cerebrovascular events, cavernous angioma and hamartoma.

Twenty patients had no information regarding the first EEG at the time of the diagnosis and 38 patients had normal EEG; diagnosis and determination of the type and classification of seizures were based primarily on the clinical data in these patients. EEG recordings were considered abnormal if EEG included both unequivocal epileptiform abnormalities and non-epileptiform abnormalities such as paroxysmal slow waves and focal/generalized background irregularities. EEG tracings at the follow-up visits 1 year after the AED withdrawal period were accepted as 'post-withdrawal EEG'.

Of 200 patients, 92 (46%) had generalized, 75 (37.5%) had partial, and 24 (12%) had mixed type of seizures; seizures in 9 (4.5%) patients could not be defined from the available data. Fifty-two patients (26%) had tonic, 51 (25.5%) had complex partial, 16 (8%) had simple partial, 15 (7.5%) had atonic, 12 (6%) had tonic-clonic, 9 (4.5%) had absence, 8 (4%) had secondarily generalized, and 3 (1.5%) had myoclonic seizures, and 1 patient (0.5%) had epileptic spasms.

Fifty-eight of the patients (29%) were classified as having idiopathic generalized epilepsy, 54 (27%) as idiopathic localization-related epilepsy, 20 (10%) as symptomatic localization-related epilepsy, 8 (4%) as symptomatic generalized epilepsy, 5 (2.5%) as cryptogenic generalized epilepsy, and 2 (1%) as cryptogenic localization-related epilepsy. One patient (0.5%) was diagnosed as reflex epilepsy (idiopathic hot water epilepsy with simple partial and autonomic symptoms). Fifty-two patients could not be classified because of inadequate clinical data and/or neuroimaging studies or discrepancy between seizure type and laboratory studies. Because of the relatively small number of patients in the subgroups, seizure types were classified as generalized, partial or mixed type of seizures and etiological epilepsy classification was simplified as symptomatic-cryptogenic (in the same group) or idiopathic epilepsy.

Epileptic syndromes could be defined in only 38 patients. Of these, 22 patients had benign childhood epilepsy with centro-temporal spikes, 7 had juvenile myoclonic epilepsy, 5 had temporal lobe epilepsy (all symptomatic), 1 had cryptogenic childhood epilepsy with occipital paroxysms, 2 had frontal lobe epilepsy (without any apparent etiology), and 1 had Lennox–Gastaut syndrome.

Regarding AED therapy before withdrawal, 156 patients (78%) were treated by only 1 AED (66 by valproic acid, 57 by carbamazepine, 29 by phenobarbital, 3 by phenytoin, 1 by ethosuximide), 32 patients (16%) by 2 AED, 10 patients (5%) by 3 AED, 1 patient (0.5%) by 4 AED, and 1 patient (0.5%) by 5 AED. At the time of withdrawal, only 4 patients were on combination therapy with more than 1 AED. In these patients, the latest drug was reduced first and after its complete discontinuation, reduction of the second drug was started, and so on until all drugs were withdrawn. AED withdrawal was generally decided when patients had at least a 2-year (mean: 40.3 months) seizure-free period and a normal EEG.[1,2,8] All but 4 patients had EEG within 1 year before withdrawal and 39 patients had abnormal EEG tracings, 10 of which consisted of definite epileptiform abnormalities other than minor epileptiform abnormalities like episodic slow waves or background irregularities. Withdrawal of AED was performed generally in 6 months. The average time of withdrawal was 6.6 ± 0.1 months (min: 1 month, max: 14 months). Since this is a retrospective study, patients with a seizure-free period of less than 2 years and withdrawal period shorter or longer than 6 months were also included in the study.

Family history was accepted positive if first-degree relatives (parents and siblings) had a history of epilepsy or 1 or more unprovoked seizures.

One patient had diagnosis of Bardet–Biedl syndrome, 1 tuberosclerosis and polycystic kidney disease, 1 scoliosis, 1 tic disorder and 2 attention deficit hyperactivity disorder in addition to epilepsy.

The patients were classified in different groups to clarify the risk factors according to sex, age at onset, family history of epilepsy, history of previous febrile seizures, events in perinatal or childhood history, neurological examination, mental retardation, type of seizures, epilepsy classification, MRI, time period between the onset of first seizure and start of AED treatment, time period between the first seizure and the last seizure (active disease), time period between starting AED and last seizure (treatment response time), time period between the last seizure and withdrawal of AED treatment (seizure-free period), total duration of AED, duration of withdrawal, number of seizures prior to starting the AED treatment, number of seizures in the time period between the start of AED treatment and the last seizure, first EEG, and post-withdrawal EEG.

2.1. Statistical analysis

SPSS statistical analysis software package version 11.5 (SPSS Inc., Chicago, IL) was used in the statistical analysis. The chi-square tests were used to determine the associations between categorical data. Continuous variables were examined using Mann–Whitney U test. Associations and relative risks of variables and recurrence during follow-up were investigated by Cox regression analysis. Multivariate Cox regression was performed for factors that had statistically significant values up to 20% in univariate analysis.[9] Statistical significance was accepted at $p < 0.05$ and p values between 0.05 and 0.10 were accepted as having a tendency for significance.

Table 1
Possible risk factors, clinical features and corresponding recurrence rate.

	Subjects		Recurrence rate %	*P* values
	No	%		
Sex				
Male	118	59	22	0.058**
Female	82	41	34.1	
Age at onset				
<6 years	91	45.5	24.2	>0.05
≥6 years	109	54.5	29.4	
Family history of epilepsy				
Positive	29	14.5	27.6	>0.05
Negative	171	85.5	26.9	
History of febrile seizures				
Positive	40	20	20	>0.05
Negative	160	80	28.8	
Perinatal/childhood history				
Positive	63	31.5	20.6	>0.05
Negative	137	68.5	29.9	
Neurological examination				
Positive	19	9.5	31.6	>0.05
Negative	181	90.5	26.5	
Mental retardation				
Positive	18	9	38.9	>0.05
Negative	182	91	25.8	
MRI				
Abnormal	35	23.5	40	>0.05
Normal	114	76.5	28.1	
Type of seizure				
Generalized	92	48.2	28.3	>0.05
Partial	75	39.3	30.7	
Mixed	24	12.6	20.8	
Etiological epilepsy classification				
Idiopathic	112	76.2	31.3	>0.05
Symptomatic-cryptogenic	35	23.8	31.4	
Time between the onset of first seizure and the onset of AED treatment				
0–2 months	101	50.5	31.7	>0.05
2–12 months	51	25.5	21.6	
≥12 months	48	24	22.9	
Active disease				
0–6 months	95	47.5	29.5	>0.05
6–12 months	27	13.5	22.2	
>12 months	78	39	25.6	
Treatment response time				
0–2 months	116	58	30.2	>0.05
2–12 months	36	18	19.4	
≥12 months	48	24	25	
Total duration of withdrawal				
1–6 months	106	53	32.1	>0.05
>6 months	94	47	21.3	
Total number of AED before remission				
1	154	77	29.9	>0.05
2	32	16	18.8	
≥3	14	7	14.3	
Number of seizures before starting AED treatment				
1–5	145	72.5	54.9	>0.05
6–10	9	4.5	22.2	
>10	46	23	23.9	
Number of seizures after AED treatment				
No seizure	112	56	31.3	>0.05
1–5	43	21.5	37.2	
6–10	10	5	10	
>10	35	17.5	22.9	
First EEG				
Normal	38	21.1	31.6	>0.05
Abnormal	142	78.9	23.9	
Pre-withdrawal EEG				
Normal	157	80.1	27.4	>0.05
Abnormal	39	19.9	23.1	
Post-withdrawal EEG				
Normal	124	79	16.1	0.05*
Abnormal	33	21	33.3	

* Statistically significant.
** Tendency for statistical significance.

3. Results

Seizures recurred in 54 patients (27%). Twelve patients (6%) had recurrence in the first 3 months after the withdrawal, 16 (8%) in the 3–9 months period, 10 (5%) in the 9–15 months period, 2 (1%) in the 15–24 months period, and 14 (7%) had recurrence after 2 years. The mean follow-up period after AED withdrawal was 47.7 ± 39.3 months (min: 12 months, max: 172 months) in patients without seizure recurrence and 18.6 ± 24.9 months (min: 0.25 months, max: 126 months) in the patients with recurrence. The patient with the longest lapse till recurrence after withdrawal had problems during labor, the first seizure occurred at the age of 1.5 months and periventricular leukomalacia was present on MRI.

The general characteristics, clinical features and possible risk factors of the patients are shown in Table 1.

Girls were determined more likely to have a seizure recurrence than boys, and the difference approached statistical significance ($p = 0.058$).

With respect to post-withdrawal EEG recordings, patients with recurrence more frequently had abnormal EEGs than those without recurrence in the follow-up period after withdrawal, and the difference was statistically significant ($p = 0.05$, continuous correction).

The seizure-free period was significantly shorter in patients with recurrence (median: 35 months; min: 7 months, max: 65 months) than in patients without recurrence (median: 36 months; min: 12 months, max: 113 months) ($p = 0.032$).

Patients with seizure recurrence had a significantly shorter total duration of AED treatment (36.5 months; min: 12 months, max: 210 months) than those without seizure recurrence (44.5 months; min: 7.5 months, max: 145 months) ($p = 0.013$).

With respect to post-withdrawal EEG recordings, patients with recurrence more frequently had abnormal EEGs than those without recurrence in the follow-up period after withdrawal, and the difference was statistically significant ($p = 0.05$, continuous correction).

No other factors were statistically significant.

Cox regression for univariate analysis was performed to investigate the associations between the risk factors and clinical outcome. Table 2 shows the possible risk factors demonstrating statistical significance or approaching significance.

In the multivariate Cox regression analysis, female gender and presence of abnormal post-withdrawal EEG were the risk factors determined as having an influence on seizure recurrence (Table 3) (Figs. 1 and 2). Female gender was determined as the main risk factor for recurrence after AED withdrawal in our study.

4. Discussion

The recurrence rate after discontinuation of AED therapy was 27% in our study, which is consistent with other studies showing

Table 2
Possible risk factors and relative risk (RR) of recurrence in univariate analysis.

Variables	RR	95% CI	*P* value
Sex (female)	1.93	1.12–3.30	$p = 0.017$
MRI (abnormal)	1.50	0.79–2.84	$p = 0.21$
First EEG (abnormal)	0.66	0.34–1.28	$p = 0.22$
Post-withdrawal EEG (abnormal)	2.09	0.99–4.36	$p = 0.05$
Total time of AED treatment	0.99	0.98–1	$p = 0.13$
Seizure-free period	0.98	0.96–0.99	$p = 0.016$

Table 3
Relative risk (RR) of recurrence—multivariate Cox regression.

Variables	RR	95% CI	*P* value
Sex (female)**	2.88	1.34–6.18	$p = 0.007$*
EEG after withdrawal (abnormal)	2.38	1.13–5.02	$p = 0.022$*
Total time of AED treatment	0.99	0.97–1.03	$p = 0.910$
Seizure-free period	0.98	0.94–1.02	$p = 0.269$

* Statistically significant.
** Main factor.

that approximately 70–80% of children will remain seizure-free after withdrawal of medication.[1–7,10–12] The relapse rate was even lower if patients with abnormal EEG before withdrawal, abnormal neurological signs and epileptic syndromes known to have a poor prognosis were excluded.[1] Recurrences occurred mostly in the first 2 years in our patients, as reported previously.[1,2,11,12]

Female gender was a significant risk factor in univariate and multivariate analyses in our study and was the main factor influencing the recurrence rate in multivariate analysis; however, we could not determine any reason for this gender difference when all the risk factors were analyzed according to gender (data not shown). Similar to our results, Altunbaşak et al.[1] and Dooley et al.[13] found that female gender was a significant risk factor for relapse. Gender has usually been reported to have no influence on the relapse risk.[2,4,5,11–14] This discrepancy may result from the differences in the study populations and study designs in other studies or because of our limitation in obtaining data about neuroimaging studies or classification of epilepsy syndromes in some of the patients.

In recent years, there has been a general acceptance of at least a 2-year seizure-free period before AED withdrawal,[1,2,4] although

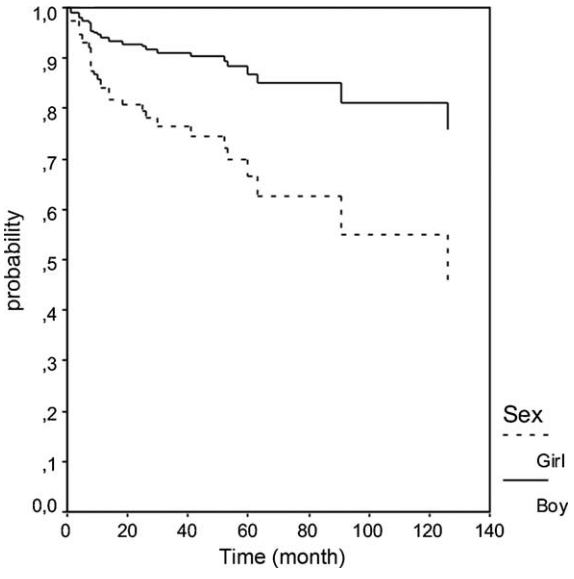

Fig. 1. Effect of sex on the probability that patients will remain seizure-free after discontinuation of AED.

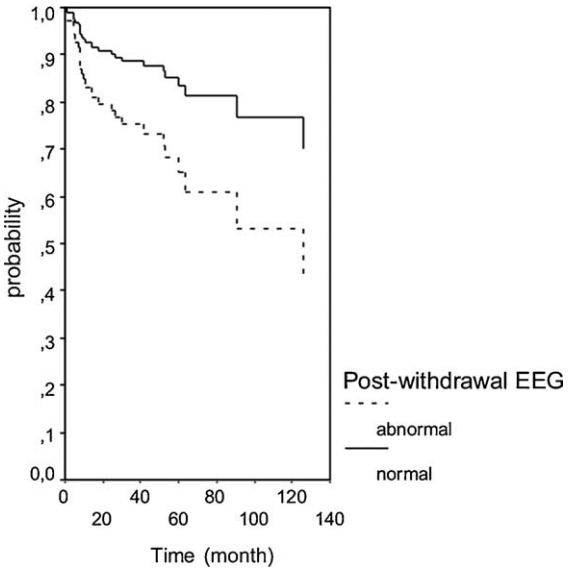

Fig. 2. Effect of post-withdrawal EEG abnormality on the probability that patients will remain seizure-free after discontinuation of AED.

seizure-free periods shorter than 4 years have also been reported as a risk factor for seizure recurrence in children.[14–16] In a prospective randomized study, after early withdrawal of AED at 6 and 12 months of therapy, 49% versus 48% of children were seizure-free at 2 years, respectively.[17] While early withdrawal may prevent the unnecessary side effects of AED therapy and lower the stress of medication on both patients and families, it can increase the risk of recurrence. Although the seizure-free period has not been found as a significant risk factor in most of the studies, in a prospective study with 433 patients, AED were withdrawn after 2, 3, 4 seizure-free years and patients were observed at least 3 years.[14] The rate of relapse was strongly associated with the duration of the seizure-free period and the risk of relapse significantly decreased only after a seizure-free period of 3 years without restriction of all types of seizure and at least 3 years of seizure-freedom was suggested like some other studies.[14,16] Our results also showed that a seizure-free period and total duration of AED treatment of more than 3 years are important factors influencing the recurrence rate, consistent with some studies.[5,14,16]

Results from the studies about age at onset of first seizure are controversial. Altunbaşak et al.[1] found less than 2 years of age at onset as a good prognostic factor in his study, in which epileptic syndromes with bad prognosis were excluded, whereas Emerson et al.[18] found age at onset related with seizure recurrence. Age at onset of more than 12 years was reported as a risk factor for recurrence by Shinnar et al.[5] and Peters et al.[17] Bouma et al.[2] reported a good prognosis for patients with no abnormal neurological signs or mental retardation and with onset of seizure at more than 5 years of age. On the other hand, some authors reported results similar to ours, that age at onset had no influence on seizure recurrence.[12,14] We did not find age at onset as a significant risk factor, perhaps due to the unselected group comprising our patient population that included both benign epilepsies and epilepsies known as having poor prognosis.

Family history of epilepsy was reported as a risk factor in idiopathic epileptic patients by Shinnar et al.[5], but it was not found as a risk factor in our study, which is consistent with some of the studies.[1,2,19] History of febrile convulsions was also not found as a risk factor in our study, and this also supports the results of other studies.[1,2,19]

Abnormal neurological examination and mental retardation of varying degree can be related to recurrence,[2,5,7,13–15] but this was

not determined in our study and some of the others.[1,15,18] This may be attributed to the fact that only 2 patients in our study had a moderate degree of mental retardation; the others had mild mental retardation.

Gherpelli et al.[12], Todt[14] and Emerson et al.[18] found the number of seizures before seizure control important for seizure recurrence. Duration of active disease (greater than 2 to 6 years before seizure control) and time lapsed between the first seizure and onset of AED treatment have been reported as risk factors in a few studies.[12,15,20,21] Polytherapy has been found as a risk factor in a selected population with partial epilepsy.[19] Factors related to seizure severity prior to achieving full seizure control (seizure frequency before AED treatment, seizure frequency while on AED treatment until seizure control, time lapse between the onset of first seizure and the onset of AED treatment, treatment response time [time elapsed from the onset of AED treatment to full seizure control] and number of AED before full remission) were not determined to be significant for seizure recurrence in our study, as reported in other studies.[1,15,16]

We found no difference between the groups of patients with AED tapering period of more versus less than 6 months, like Serra et al.[3], who compared the tapering duration of 1-month to a 6-month period. However, tapering duration of less than 6 months has also been reported as a significant risk factor.[14] The lack of a consensus in the literature may be related to limited data with respect to these factors.

We did not find any significant difference according to seizure types. Shinnar et al.[5] reported no difference between the complex partial and tonic-clonic seizures in the idiopathic and remote symptomatic patient groups, but presence of absence seizures increased the risk of seizure recurrence in the remote symptomatic group. Todt[14] found partial epilepsies and mixed type of seizures as a risk factor, but Matricardi et al.[15] reported that infantile spasms and childhood absence epilepsy carried a greater risk of relapse after AED withdrawal. In contrast, having only absence seizures has been reported as a predictor of excellent prognosis.[6] We think the differences reported regarding the effect of seizure type can be attributed to differences in the study designs and characteristics of the studied populations.

Etiology of seizures has also been related to increased risk of recurrence after AED withdrawal. The remote symptomatic epilepsy group has been most significantly related to higher relapse rates when compared to the idiopathic group.[5,14–17] No difference was found in the other studies.[1,2,13] In our study as well, etiology, either symptomatic–cryptogenic or idiopathic, was not identified as a possible risk factor.

Studies have reported conflicting results about the role of epileptiform abnormalities on EEG in predicting the recurrence rate. It has been found as both a prognostic factor[5,10,12] and a non-prognostic factor.[1,2,16] We showed no effect on seizure recurrence of the first EEG at the time of diagnosis or of the EEG obtained before the withdrawal. The conflicting results about EEG may be due to definitions of abnormal EEG. Shinnar et al.[5] found that only slowing on the first EEG, whether focal or generalized in the idiopathic epilepsy group, had a higher risk of recurrence, while significant epileptiform EEG abnormalities were not associated with a higher risk of recurrence. Altunbaşak et al.[1] included patients with normal EEG and with minor epileptiform abnormalities like episodic slow waves and could not determine EEG to be predictive for relapse. An abnormal EEG consisting of spikes, sharp waves, polyspikes and spikes and slow waves in the year before discontinuation of AED increased the relapse risk in other studies.[12,15,16] In addition, paroxysmal features appearing or persisting in the course of the disease were reported as a good predictor of relapse.[15] Most of the studies have not considered EEG abnormalities after withdrawal of AED. We found the EEG obtained after rather than before withdrawal of medication to be important in predicting the recurrence rate in our study in both bivariate and multivariate analyses. Similarly, Todt[14] and Verrotti et al.[19,22] determined the post-withdrawal EEG to be predictive of the recurrence rate. EEG recordings after withdrawal can be suggested in the follow-up period, although starting medication based on EEG abnormality is questionable. Nevertheless, it can help in accurate counselling of the patient and the family regarding prognosis.

5. Conclusion

In our study, overall recurrence rate was 27% in children, and most occurred during the first 2 years. The main factor for predicting risk of recurrence was female gender. EEG obtained after withdrawal was the other factor important for predicting risk of recurrence. Total duration of AED treatment and the seizure-free period were important risk factors. Based on the results of our study, we suggest a seizure-free period of at least 3 years on AED medication, close follow-up of female patients, and being cautious about the abnormalities on EEG recordings obtained during follow-up after withdrawal of AED treatment regarding prognosis.

Disclosure

This study was presented as an oral presentation by Dr. Akgun OLMEZ in the 7th Congress of the European Pediatric Neurology Society, 26–29 September 2007, Kusadasi, Turkey.

References

1. Altunbaşak S, Artar O, Burgut R, Yildiztaş D. Relapse risk analysis after drug withdrawal in epileptic children with uncomplicated seizures. *Seizure* 1999;**8**:384–9.
2. Bouma PA, Peters AC, Arts RJ, Stijnen T, Van Rossum J. Discontinuation of antiepileptic therapy: a prospective study in children. *J Neurol Neurosurg Psychiatry* 1987;**50**:1579–83.
3. Serra JG, Montenegro MA, Guerreiro MM. Antiepileptic drug withdrawal in childhood: does the duration of tapering off matter for seizure recurrence? *J Child Neurol* 2005;**20**:624–6.
4. Bouma PA, Peters AC, Brouwer OF. Long term course of childhood epilepsy following relapse after antiepileptic drug withdrawal. *J Neurol Neurosurg Psychiatry* 2002;**72**:507–10.
5. Shinnar S, Berg AT, Moshé SL, Kang H, O'Dell C, Alemany M, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Ann Neurol* 1994;**35**:534–45.
6. Geerts AT, Niermeijer JM, Peters AC, Arts WF, Brouwer OF, Stroink H, et al. Four-year outcome after early withdrawal of antiepileptic drugs in childhood epilepsy. *Neurology* 2005;**64**:2136–8.
7. Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz P, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. *Brain* 2004;**127**:1774–84.
8. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;**30**:389–99.
9. Winckler MI, Rotta NT. Clinical and electroencephalographic follow-up after a first unprovoked seizure. *Pediatr Neurol* 2004;**30**:201–6.
10. Wallis WE. Withdrawal of anticonvulsant drugs in seizure-free epileptic patients. *Clin Neuropharmacol* 1987;**10**:423–33.
11. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology* 1994;**44**:601–8.
12. Gherpelli JL, Kok F, dal Forno S, Elkis LC, Lefevre BH, Diament AJ. Discontinuing medication in epileptic children: a study of risk factors related to recurrence. *Epilepsia* 1992;**33**:681–6.
13. Dooley J, Gordon K, Camfield P, Camfield C, Smith E. Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: a prospective study. *Neurology* 1996;**46**:969–74.
14. Todt H. The late prognosis of epilepsy in childhood: results of a prospective follow-up study. *Epilepsia* 1984;**25**:137–44.
15. Matricardi M, Brinciotti M, Benedetti P. Outcome after discontinuation of antiepileptic drug therapy in children with epilepsy. *Epilepsia* 1989;**30**:582–9.
16. Hawash KY, Rosman NP. Do partial seizures predict an increased risk of recurrence after antiepilepsy drugs are withdrawn? *J Child Neurol* 2003;**18**:331–7.

17. Peters AC, Brouwer OF, Geerts AT, Arts WF, Stroink H, van Donselaar CA. Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy. *Neurology* 1998;**50**:724–30.
18. Emerson R, D'Souza BJ, Vining EP, Holden KR, Mellits ED, Freeman JM. Stopping medication in children with epilepsy: predictors of outcome. *N Engl J Med* 1981;**304**:1125–9.
19. Verrotti A, Morresi S, Cutarella R, Morgese G, Chiarelli F. Factors associated with relapse after antiepileptic drug withdrawal in a selected population with partial epilepsy. *Dev Med Child Neurol* 1999;**41**:643–5.
20. Specchio LM, Tramacere L, La Neve A, Beghi E. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. *J Neurol Neurosurg Psychiatry* 2002;**72**:22–5.
21. Ohta H, Ohtsuka Y, Tsuda T, Oka E. Prognosis after withdrawal of antiepileptic drugs in childhood-onset cryptogenic localization related epilepsies. *Brain Dev* 2004;**26**:19–25.
22. Verrotti A, Morresi S, Cutarella R, Morgese G, Chiarelli F. Predictive value of EEG monitoring during drug withdrawal in children with cryptogenic partial epilepsy. *Neurophysiol Clin* 2000;**30**:240–5.