

Determination of Risk Factors Associated with Seizure Relapse after Antiepileptic Drug Withdrawal

Research Article

Sebahattin Vurucu*, Mehmet Saldir, Bulent Unay, Ridvan Akin

*Department of Pediatric Neurology, Gulhane Military Medical Academy,
06018 Etlik, Turkey*

Received 29 November 2008; Accepted 22 March 2009

Abstract: There is no consensus regarding the time of antiepileptic drug withdrawal and the relevant risk factors for seizure relapse. In this study, we aimed to determine the seizure relapse rates and the associated risk factors for seizure relapse in childhood epilepsy. Two-hundred sixty-six epileptic patients who discontinued the antiepileptic drug therapy after a seizure-free period of at least two years, were enrolled into the study. The data of the patients regarding sex, febrile convulsion history, family history, age at onset, type of epilepsy, total number of seizures and antiepileptic drugs, seizures during treatment, mental status, first and last electroencephalography, brain imaging findings, etiological factors and seizure relapse in the first two years after antiepileptic drug withdrawal were obtained from the patients' files. Univariate logistic regression analysis was performed for each variable. The variables which were found to be statistically significant in univariate analysis, were included in multivariate logistic regression analysis. The overall seizure relapse rate after antiepileptic drug withdrawal was 19.2%. There were no significant differences for seizure relapse rate after antiepileptic drug withdrawal between patient groups with respect to sex, family history, type of epilepsy, febrile convulsion history, seizures before treatment, first electroencephalography findings, brain imaging findings and etiology. However, there were statistically significant differences for seizure relapse rate among patient groups concerning age at onset of epilepsy, new seizure during treatment, the total number of antiepileptic drugs, mental status, and last electroencephalography findings. We imply that the clinical status of the patients should be considered before the cessation of drug therapy rather than the etiological factors or laboratory findings.

Keywords: Antiepileptic drug withdrawal • Seizure relapse • Risk factors • Children

© Versita Sp. z o.o.

1. Introduction

Worldwide ten and a half million children under the age of 15 years are estimated to have epilepsy. In developed countries and developing countries, the annual incidence rate of 41-50/100 000 and 61-124/100 000 have been reported respectively [1,2]. Cumulative incidence studies under 15 year old children indicate that 1.0-1.7% of children have had at least one seizure and 0.7-0.8% have had recurrent seizures [1-3,4]. Overall, 70-80% of epileptic children reach complete remission with antiepileptic therapy with a better prognosis than epileptic adults even after treatment discontinuation [5-7]. However, there is no consensus regarding the time of withdrawal and the relevant risk factors in terms of seizure relapse [5,8,9]. The most important point to

withdraw antiepileptic drugs (AEDs) is the presence of a seizure free period of at least two years in an epileptic patient. The relapse rates in childhood-onset epilepsy have been reported as 22.4-40.0% after AEDs withdrawal [10-14]. Thus, determination of the risk factors for relapse after AEDs withdrawal is crucial to minimize the seizure relapse rates. In this study, we aimed to determine the seizure relapse rates and the associated risk factors after AEDs withdrawal in childhood epilepsy.

2. Material and Methods

Two hundred sixty-six epileptic pediatric patients who discontinued the AED therapy after a period of at least two years seizure-free period, and had a follow-up an additional two years after were enrolled in the study. This

* E-mail: sebahattinvurucu@yahoo.com

is a long term retrospective analysis. The patients' data regarding sex, febrile convulsion history, family history, age at onset and type of epilepsy, total number of seizures and AEDs, seizures during treatment, mental status, first and last electroencephalography (EEG) findings, brain magnetic resonance imaging findings, etiological factors for epilepsy and seizure relapse in the first two years after AEDs withdrawal were obtained from the patients' files. Age at onset of epilepsy were designated as <2 years, 2-5 years, and >5 years. The total number of seizures before treatment were designated as 1, 2 and >2. Epilepsy types were classified as partial or generalized according to International League Against Epilepsy. EEG findings were classified as normal, generalized, and focal. Mental status was evaluated as normal or abnormal according to neurological examination, Denver Developmental Screening Test, and Weschler Intelligence Scale for Children.

SPSS for Windows version 11.5 was used for statistical analysis. Univariate logistic regression analysis was performed for each variable. Odd's ratio, 95% Confidence Intervals and significance levels were calculated. The variables, which were found to be statistically significant in univariate analysis, were included in multivariate logistic regression analysis. Backward LR Multivariate logistic regression analysis was performed to determine probable risk factors associated with seizure relapse after AEDs withdrawal. Statistical significance level was set at $p < 0.05$.

3. Results

The overall seizure relapse rate after AEDs withdrawal was 19.2%. Demographic features and statistical results of the patients for seizure relapse are summarized in Table 1. According to univariate logistic regression analysis, there were no significant differences for seizure relapse rate after AEDs withdrawal between patient groups with respect to sex, febrile convulsion history, family history and type of epilepsy, seizures before treatment, first EEG findings, brain imaging findings and etiology ($p > 0.05$). However, there were significant differences for seizure relapse rates between patient groups with respect to age at onset of epilepsy (OR=0.398, 95%CI=0.176-0.899) and the total number of seizures (OR=16.258, 95%CI=2.121-124.597), new seizure during treatment (OR=3.219, 95%CI=1.718-6.030), the total number of AEDs (OR=8.548, 95%CI=4.359-16.763), mental status (OR=2.581, 95%CI=1.214-5.486), and generalized abnormalities in the last EEG findings (OR=4.286, 95%CI=1.233-14.901). According to multivariate logistic

regression analysis the total number of AEDs was determined the only and the most important risk factor associated with seizure relapse after AED withdrawal (OR=30.016, 95%CI=7.419-121.441).

4. Discussion

In recent years, many studies have been done in epileptic children for determining the parameters for and especially the risk factors affecting seizure relapse after AEDs withdrawal. Yet, there is no consensus concerning the conditions for discontinuation of AEDs. Long-term antiepileptic therapy displays various adverse effects. Therefore, both the seizure relapse risk and the side effects of AEDs alike should be kept in mind while deciding on AEDs withdrawal.

Seizure relapse rates after AEDs withdrawal have been reported as 22.4-40.0% and 85-90% of all those relapses that occur in the first two years of withdrawal [10-15]. Accordingly, children should be followed closely during the first two years after AEDs withdrawal. Altunbaşak *et al.* reported the seizure relapse rate as 20.6% in children with uncomplicated epilepsy, and they claimed that the low rate was associated with the absence of neurological deficits, mental retardation and EEG abnormalities at the time of treatment discontinuation [14]. In our study, overall seizure relapse rate after AED withdrawal was 19.2%. Our relatively lower rate can be attributed to the high number of patients with low risk factors present in the study group.

The results in terms of the effect of sex on seizure relapse rate were inconsistent. Altunbaşak *et al.* reported the seizure relapse rate as 30.8% in females and 13.8% in males [14]. They also mentioned that female sex was an important risk factor for seizure relapse. We found the seizure relapse rate as 20.7% in females and 18.1% in males and there was no significant difference between them.

There are some reports suggesting that the history of epilepsy in the family or previously experienced febrile convulsions is risk factors for seizure relapse [16-17]. We found no significant association between seizure relapse rates and the family history of epilepsy or the previous febrile convulsions.

Epileptic syndromes are completely different from one other according to remission rates. For example, although remission rate is 100% in benign rolandic epilepsy, it is much lower in juvenile myoclonic epilepsy and West Syndrome. In one study, it was reported that idiopathic epilepsies had higher remission rates than cryptogenic and symptomatic epilepsies [18,19]. It is claimed that the factors associated with remission

Table 1. Demographic features of the patients and the relationship between relapse ratios and risk factors.

	n (%)	No relapsen (%)	Relapsen (%)	OR	95%CI	p
Sex						
Male	155 (58,3)	127 (81.9)	28 (18.1)	R		
Female	111 (41,7)	88 (79.3)	23 (20.7)	1.19	0.64-2.19	0.59
Family history of epilepsy Family						
Yes	35 (13,2)	30 (85.7)	5 (14.3)	R		
No	231 (86,8)	185 (80.1)	46 (19.9)	0.67	0.25-1.82	0.43
Febrile convulsion						
Yes	67 (25,2)	55 (82.1)	12 (17.9)	R		
No	199 (74,8)	160 (80.4)	39 (19.6)	0.90	0.44-1.83	0.76
Age at onset of epilepsy						
<2	111 (41,7)	82 (73.9)	29 (26.1)	R		
2-5	82 (30,8)	69 (84.1)	13 (15.9)	0.53	0.26-1.10	0.09
>5	73 (27,4)	64 (87.7)	9 (12.3)	0.40	0.18-0.90	0.03
Epilepsy type						
Partial	77 (28,9)	61 (79.2)	16 (20.8)	R		
Generalized	189 (71,19)	154 (81.5)	35 (18.5)	0.87	0.45-1.68	0.67
Total number of seizures						
1	37 (13,9)	36 (97.3)	1 (2.79)	R		
2-5	139 (52,3)	117 (84.2)	22 (15.8)	6.77	0.88-51.98	0.07
>5	90 (33,8)	62 (68.9)	28 (31.1)	16.26	2.12-124.60	0.08
Seizures before treatment						
1	65 (24,5)	50 (76.9)	15 (23.1)	R		
2	72 (27,2)	54 (75)	18 (25)	1.11	0.51-2.44	0.79
>2	128 (48,3)	110 (85.9)	18 (14.1)	0.55	0.25-1.17	0.12
New seizure during treatment						
Yes	87 (32,7)	59 (67.8)	28 (32.2)	R		
No	179 (67,3)	156 (87.2)	23 (12.8)	3.22	1.72-6.03	0.01
AED treatment						
Monotherapy	202 (75,9)	182 (90.1)	20 (9.9)	R		
Polytherapy	64 (24,1)	33 (51.6)	31 (48.4)	8.55	4.36-16.76	0.01
Mental status						
Normal	95 (65,1)	76 (80)	19 (20)	R		
Abnormal	51 (34,9)	31 (60.8)	20 (39.2)	2.58	1.21-5.49	0.01
First EEG						
Normal	60 (22,6)	53 (88.3)	7 (11.7)	R		
Generalized abnormality	98 (36,8)	76 (77.6)	22 (22.4)	2.19	0.87-5.50	0.10
Focal abnormality	108 (40,6)	86 (79.6)	22 (20.4)	1.94	0.77-4.85	0.16
Last EEG						
Normal	133 (81,1)	114 (85.7)	19 (14.3)	R		
Generalized abnormality	12 (7,3)	7 (58.3)	5 (41.7)	4.29	1.23-14.90	0.02
Focal abnormality	19 (11,6)	14 (73.7)	5 (26.3)	2.14	0.69-6.64	0.19
Brain imaging findings						
Normal	170 (70,5)	141 (82.9)	29 (17.1)	R		
Abnormal	71 (29,5)	54 (76.1)	17 (23.9)	1.53	0.78-3.01	0.28
Etiology						
Idiopathic	161 (60,5)	132 (82)	29 (18)	R		
Symptomatic	105 (39,5)	83 (79)	22 (21)	1.21	0.65-2.24	0.55

.....OR: Odd's Ratio R: Reference.....

may influence the seizure relapse rates after AEDs withdrawal. Ohta *et al.* reported the overall seizure relapse rates after AEDs withdrawal as 9.8% in children with cryptogenic epilepsy [5]. The relapse rates were lower in early onset cryptogenic epilepsy than in early onset symptomatic epilepsy [20]. In this study, seizure relapse rates were higher in symptomatic epileptic patients when compared with the idiopathic epileptic group. However, the difference did not reach statistical significance. We did not find any significant difference for seizure relapse rates between the patients with normal and abnormal brain imaging findings neither.

Reported in the literature that seizure relapse rates were different according to epilepsy types; being lower in simple partial epilepsy [21]. In this regard, our findings did not show any difference between patients with generalized and partial epilepsy.

In the literature there are several studies with contradictory results which have investigated the effects of several factors, i.e. the number of seizures before treatment, the total number of seizures, the time period from the initiation of treatment until the convulsions being under control, the duration of discontinuation and seizure relapse rates after AED withdrawal [5,14,22]. It has been reported that the overall seizure relapse rate was 23-71% in patients who did not receive any treatment after the first seizure and seizure relapse rates were higher in patients who had abnormal EEG findings and symptomatic epilepsy [23-28]. The relation between age at onset of epilepsy and seizure relapse rates have been investigated in several studies with contradictory results [10,11,29]. The children who had the first seizure before six year-old had higher rates of family history of epilepsy and febrile convulsion, but had lower seizure relapse rates after AED withdrawal [5]. Emerson *et al.* reported that the patients who had the first seizure before two year-old had higher seizure relapse rates than those who had the first seizure after two year-old [10]. On the other hand, Altunbaşak *et al.* reported that patients who had the first seizure before they reached two years old showed better prognosis [14]. Berg and Shinnar reported that the epilepsies, which began before 12 years old age, had higher rate of seizure relapse risk than those after 12 years of age [30]. Shinnar *et al.* also reported that the mean age of epilepsy was 6.9 years in patients who

had seizure relapse and 4.3 years in patients who did not have seizure relapse [31]. In our study, we found that age at the onset of epilepsy (especially >5 years), the total number of seizures (especially >5 seizure), new seizure during treatment, and the need for polytherapy were important risk factors for seizure relapse after AEDs withdrawal.

Some studies have mentioned higher or lower seizure relapse rates in epileptic patients with mental retardation. Emerson *et al.* reported that epileptic patients with mental retardation had higher relapse rates than those without mental retardation [10]. It has been said that the first EEG findings had no value to predict the prognosis [32-34]. In this study, we found that patients with mental retardation had a higher risk for seizure relapse after AEDs withdrawal than the ones who had normal mental status. We found that the first EEG findings were not risk factors for seizure relapse. However, we found that patients who had generalized abnormality in their last EEG had higher risk for seizure relapse than patients who had normal EEG.

Many variables, which were found to be statistically significant in univariate logistic regression, were not found statistically significant after adjustment by other variables in multivariate analysis. The most important reason of this situation is multicollinearity. Due to that, we didn't use some variables in terminal model. On the other hand, relations in some variables are two sided. We couldn't evaluate which variable was the cause or the outcome; for example relation between multi drug use or abnormal EEG finding and AED.

In conclusion, the risk factors associated with seizure relapse after AEDs withdrawal in epileptic patients are of paramount importance for the decision of treatment discontinuation. In our study, we found that early age at onset of epilepsy (<2 years), more seizure numbers (>5 years), mental retardation, and the need for polytherapy were important risk factors for seizure relapse after AEDs withdrawal. Therefore, rather than the etiological factors or laboratory findings, we imply that the clinical status of the patient should be considered before the cessation of drug therapy. The retrospective nature of this study is a limitation factor and clarifying risk of seizure relapse after AEDs withdrawal needs prospective studies.

References

- [1] Guerrini R., Epilepsy in children. *Lancet*, 2006, 367, 499-524
- [2] Forsgren L., Epidemiology in epilepsy. *Epilepsy primarily affects small children and the elderly.* *Lakartidningen*, 1997, 94, 1899-1902
- [3] Hauser WA., Annegers J.F., Kurland L.T., Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*, 1993, 34, 453-468

- [4] Tsuboi T., Prevalence and incidence of epilepsy in Tokyo. *Epilepsia*, 1988, 29, 103–110
- [5] 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
- [6] Sillanpää M., Remission of seizures and predictors of intractability in long-term follow-up. *Epilepsia*, 1993, 34, 930–936
- [7] Holowach J., Thurston D.L., O'Leary J., Prognosis in childhood epilepsy: follow-up study of 148 cases in which therapy had been suspended after prolonged anticonvulsant control. *N. Engl. J. Med.*, 1972, 286, 169–174
- [8] Aicardi J., *Epilepsy in children*, second ed., Raven, New York, 1994, 402–428
- [9] Greenwood R.S., Tennison M.B., When to start and stop anticonvulsant therapy in children. *Arch. Neurol.*, 1999, 56, 1073–1077
- [10] Emerson R., D'Souza B.J., Vining E.P., Holden K.R., Mellits E.D., Freeman J.M., Stopping medication in children with epilepsy. *N. Engl. J. Med.*, 1981, 304, 1125–1129
- [11] Shinnar S., Berg A.T., Moshe S.L., Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Annals of Neurology*, 1994, 35, 534–545
- [12] Arts W.F., Visser L.H., Loonen M.C.B., Follow-up of 146 children with epilepsy after withdrawal of antiepileptic drugs. *Epilepsia*, 1988, 29, 244–250
- [13] Tennison M., Greenwood R., Lewis D., Thorn M., Discontinuing antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month taper period. *N. Engl. J. Med.*, 1994, 330, 1407–1410
- [14] Altunbasak S., Artar O., Burgut R., Yildiztas D., Relapse risk analysis after drug withdrawal in epileptic children with uncomplicated seizures. *Seizure*, 1999, 7, 384–389
- [15] Mastropolo C., Tondi M., Carboni F., Manca S., Zoroddu F., Prognosis after therapy discontinuation in children with epilepsy. *European Neurology*, 1992, 32, 141–145
- [16] Daoud A.S., Ajloni S., El-Salem K., Horani K., Ootom S., Daradkeh T., Risk of seizure recurrence after a first unprovoked seizure: a prospective study among Jordanian children. *Seizure*, 2004, 13, 99–103
- [17] Donati F., Hassink R.I., Jung H., Vassella F., Factors predicting the risk of relapse after antiepileptic drug discontinuation in children with partial seizures. *Eur. J. Pediatr.*, 1995, 154, 44–47
- [18] Sillanpää M., Jalava M., Kaleva O., Shinnar S., Long-term prognosis of seizures with onset in childhood. *N. Engl. J. Med.*, 1998, 338, 1715–1722
- [19] Berg A.T., Shinnar S., Levy S.R., Testa S.M., Testa F.M., Smith-Rapaport S., et al., Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. *Epilepsia*, 2001, 42, 1553–1562
- [20] Gross-Tsur V., Shinnar S., Discontinuing antiepileptic drug treatment. In: Wyllie E., editor. *The treatment of epilepsy: principles and practice*, second ed. Baltimore, MD: Williams and Wilkins, 1996, 799–807
- [21] Ishiguro Y., Okumura A., Nomura K., Watanabe K., Negoro T., Takada H., et al., A pilot study on benign partial epilepsy in children with complex partial seizures. *Seizure*, 2001, 10, 194–196
- [22] Gherpelli J.L., Kok F., dal Forno S., Elkis L.C., Lefevre B.H., Diament A.J., Discontinuing medication in epileptic children: a study of risk factors related to recurrence. *Epilepsia*, 1992, 33, 681–686
- [23] Scotoni A.E., Manreza M.L., Guerreiro M.M., Recurrence after a first unprovoked cryptogenic/idiopathic seizure in children: a prospective study from Sao Paulo, Brazil. *Epilepsia*, 2004, 45, 166–170
- [24] Boonluksiri P., Risk of seizure recurrence following a first unprovoked seizure in children. *J. Trop. Pediatr.*, 2003, 49, 379–381
- [25] Pearce J.L., Mackintosh H.T., Prospective study of convulsions in children. *N.Z. Med. J.*, 1979, 89, 1–3
- [26] Elwes R.D.S., Chesterman P., Reynolds E.H., Prognosis after a first untreated tonic-clonic seizure. *Lancet*, 1985, 2, 752–753
- [27] Stroink H., Brouwer O.F., Arts W.F., Geerts A.T., Peters A.C., van Donselaar C.A., The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. *Dutch study of epilepsy in childhood. J. Neurol. Neurosurg. Psychiatry*, 1998, 64, 595–600
- [28] Berg A.T., Shinnar S., The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology*, 1991, 41, 965–972
- [29] Wallis W.E., Withdrawal anticonvulsant drug in seizure-free epileptic patient. *Clin. Neuropharmacol.*, 1987, 10, 423–433
- [30] Berg A.T., Shinnar S., Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*, 1994, 44, 601–608
- [31] Shinnar S., Vining E.P., Mellits E.D., D'Souza B.J., Holden K., Baumgardner R.A., et al., Discontinuing

- antiepileptic medication in children with epilepsy after two years without seizures: a prospective study. *N. Eng. J. Med.*, 1985, 313, 976-980
- [32] Todt H., The late prognosis of epilepsy in childhood: results of a prospective follow-up study. *Epilepsia*, 1984, 25, 137-144
- [33] Foorster C., Schmidthberger G., Prognosis in childhood epilepsy after discontinuation of therapy. *Monatsschr. Kinderheilkd.*, 1992, 130, 225-228
- [34] Joul-Jensen P., Frequency of recurrence after discontinuation of anticonvulsant therapy in patients with epileptic seizures, new follow-up study after 5 years. *Epilepsia*, 1968, 9, 11-16