Original Article

Discontinuation of Antiepileptic Drugs in Children with Epilepsy: 2-year follow-up

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Background: We attempted to identify the factors associated with seizure control and recurrence after 2-year remission in children with epilepsy.
Methods and Patients: We retrospectively investigated clinical features of epileptic children with and without relapse over a 2-year period following discontinuation of antiepileptic drugs (AEDs). Features of EEGs and clinical findings were compared among 44 children with relapse and 66 children without relapse using both bivariate and multivariate analyses.
Results: Clinical features that demonstrated strong univariate association with seizure relapse included: history of status epilepticus, symptomatic focal epilepsy, and abnormal EEG at the time of AED withdrawal.
Conclusions: Our data indicated that there are three important predictors of seizure relapse: history of status epilepticus, symptomatic focal epilepsy, and abnormal EEG at the time of medication withdrawal.

Key words: Epilepsy; Children; Antiepileptic drug; Remission; Relapse

Introduction

Approximately 70% of children with epilepsy who are seizure-free for longer than 2 or 4 years, while on antiepileptic drugs (AEDs), will remain so when medications are withdrawn[1-3]. As epilepsy is a heterogeneous disorder that can be lesional or genetically linked (e.g.,*KCNQ2, KCNQ3, SCN1A*), rather than a single disease entity, some patients require drugs for continued control of seizures and some do not. There is no single, accepted duration of remission for consideration of medication withdrawal[4]. Early medication withdrawal is not recommended as a standard practice in children with epilepsy, even with a rapid response to medication. Many physicians consider 2 years to be the typical period necessary for discontinuation of medication [1,4]. Early withdrawal of AEDs may prevent unnecessarily prolonged treatment, but increase the risk of recurrence. Hence, it may be appropriate to consider in which patients medication can be safely stopped rather than when medication can be stopped[5]. As such, indicators of prognosis after discontinuation of treatment would be of considerable clinical value.

Shorvon et al.[6] reported that 12% of 108

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patients with epilepsy had a clinical course characterized by "intermittent pattern" (i.e., seizure recurrence after certain periods of a seizure-free state). More than half of the relapses occurred in children who were tapering or had completely tapered off their medications or who had never taken medication[7]. The risk of relapse after discontinuation of AEDs in unselected groups of seizure-free patients is on the order of 25% in the first year and 29% after 2 years[8].

Many factors appear to influence the degree of risk for seizure recurrence following withdrawal of medication. These include: epileptic syndromes, age at onset, underlying etiology, electroencephalogram (EEG), severity of epilepsy, and influences of individual drugs[8]. However, there has been no general agreement on the risk factors for seizure recurrence after withdrawal of medication among previous studies, perhaps due to differences in inclusion criteria, composition of the groups, duration of follow-up, and methodologies.

In this study, we attempted to identify the risk factors for seizure recurrence after discontinuation of AEDs following 2-year seizure remission in epileptic children by comparing the clinical features of children with relapse and children without relapse during 2-year follow-up period.

Patients and Methods

We retrospectively reviewed the epilepsy databases of National Cheng Kung University Hospital and Chung Shan Medical University Hospital for the period between 1997 and 2015.

We identified 107 children with epilepsy who had been treated at these hospitals and met the inclusion criteria: (a) onset of epilepsy at 15 years of age or younger, (b) seizure-free for 2 years or more, (c) discontinuation of AEDs, (d) available information about seizure manifestation, medication, and blood level of AEDs, as well as EEG findings.

These children were followed up periodically after medications were discontinued. If a seizure did occur, their AEDs were restarted at the previous dose. Based on the outcome after stopping AEDs, the patients were divided into two groups: (i) Recurrence group (RR)—seizure recurrence during the 2-year follow-up, and (ii) No Recurrence group (NR)—no seizure recurrence during the 2-year follow-up.

For each patient, we recorded sex, age at onset of epilepsy, types of seizures and epilepsy syndromes, number of seizures before treatment, seizure frequency (low: one every 4-6 months; moderate: one to two every 1-3 months; or high: more than one per month), presence of status epilepticus, febrile seizures, family history of epilepsy, presence of abnormal neurologic findings (e.g., delayed cognitive development), motor deficits, duration of treatment, number of AEDs used, duration of seizure-free period before stopping AEDs, and interval between stopping AEDs and seizure recurrence. In addition, we looked at the serial EEG findings including when epilepsy was diagnosed, when AEDs were stopped, during the follow-up after AEDs were discontinued or when seizures recurred, and at the end of the 2-year follow-up. An abnormal EEG was defined as a specific focal or generalized epileptiform or slow-wave abnormality. The types of seizures and epileptic syndromes were classified according to the Commission on Classification and Terminology of the International League Against Epilepsy[9,10]. Neuroimaging abnormalities were confirmed either on brain CT or MRI, if clinician suspected a brain lesion.

For patients with seizure recurrence, outcomes were classified as good (remission for 1 year after AED restart), fair (remission for less than 1 year after AED restart), and deteriorated (seizures more frequent than before stopping AEDs and not seizure-free even with polytherapy).

Statistical analysis

The Mann-Whitney test was used for univariate analysis of continuous variables; a χ^2 or Fisher's Exact test was used for bivariate analysis of dichotomous variables; and a stepwise Cox's hazard-function test was used for multivariate analysis to determine which factors most strongly predict seizure recurrence. Significance was set at $p < 0.05$.

Table 1. ***Comparisons of patients with and without relapse of seizures at the end of follow-up***

Characteristics	*With recurrence (n=45), n (%)*	*Without recurrence (n=66), n (%)*
Gender (male/female)	22/23	36/30
Age at onset of epilepsy		
<2 y	8 (18)	3 (5)
2-12y	32 (71)	59 (89)
>12 y	5 (11)	4 (6)
Period of reduction of AED		
≦6 m	18 (40)	28 (42)
>6 m	27 (60)	38 (58)
Type of seizure		
Partial	24 (53)	27 (41)
Generalized	21 (47)	39 (59)
Family history of epilepsy	5 (11)	6 (9)
History of febrile seizures	7 (16)	8 (12)
History of status epilepticus	**6 (13)**[#]	**1 (2)**[#]
EEG at epilepsy diagnosis		
Epileptiform EEG	40 (89)	63 (95)
Slowing EEG	12 (27)	10 (15)
Abnormal EEG at AED withdrawal	**30 (67)**[#]	**31 (47)**[#]
Abnormal EEG at the end of follow-up	24 (53)	27 (41)
Initial seizure frequency*		
High	10 (22)	13 (20)
Moderate	9 (20)	8 (12)
Low	26 (58)	45 (68)
Total no. of seizures before control		
2	3 (7)	18 (27)
3-10	32 (71)	34 (52)
>10	10 (22)	14 (21)
Mental retardation #	11 (24)	9 (14)
Neurological abnormality	12 (27)	8 (12)
Neuroimaging abnormality (if suspected lesional)	3/18 (17)	6/19 (32)
No. of AEDs		
1	32 (71)	53 (80)
2	8 (18)	9 (14)

≧3	5 (11)	4 (6)

*[#]and bold fonts indicate significance (P<0.05); P values from Fisher's exact test; AED: antiepileptic drug, # Mental retardation: IQ<70, * high: >1 seizure per month, moderate: 1-2 seizures every 1-3 months, low: one seizure every 4-6 months.*

Results

A total of 111 patients were enrolled in this study. Of these, 66 (59%) remained seizure-free throughout this study and 45 (41%) relapsed. Table 1 compares the data of those who relapsed and those who did not. There were significantly ($p<0.05$) higher rates of history of status epilepticus and abnormal EEG at AED withdrawal in patients with relapse than in those without relapse. Sixty-one of 111 patients (55 %) had an abnormal EEG at the time of AED withdrawal: 30 (67%) of 45 in the RR group and 31 (47%) of 66 in the NR group. Six (13%) of 45 in the RR group and only 1 (2%) of 66 in the NR group had a history of status epilepticus (Table 1).

In terms of the number of AEDs, among children without relapse, 53 (80%) were treated with single AED, 9 (14%) with two AEDs, and 4 (6%) with three AEDs. In contrast, 32 (71%) in RR group were treated with single AED, 8 (18%) with two AEDs, and 5(11%) with three or more than three AEDs.

Table 2 summarizes the distributions of epilepsy syndromes in both groups. Symptomatic focal epilepsy was observed more often in the RR group than in the NR group (P=0.014, OR=3.95, 95% CI :1.13-15.6). (Table 2 and Table 3)

History of status epilepticus was more frequent in the RR group than in the NR group (p=0.017, OR=10, 95% CI :1.13-466.8). Abnormal EEG at the time of AED withdrawal was significantly related to seizure recurrence, with a higher rate of abnormal EEG in the RR group than in the NR group. (P=0.031, OR=2.26, 95% CI :1.02-5.02). (Table 3)

Risk factors for relapse following withdrawal of AEDs in 45 children with epilepsy are shown in Table 3. The most important predictors of recurrence were history of status epilepticus, symptomatic focal epileptic syndrome, and abnormal EEG at the time of medication withdrawal.

Discussion

We found significant risk factors related to seizure recurrence following withdrawal of AEDs including history of status epilepticus, symptomatic focal epilepsy, and abnormal EEG at the time of AED withdrawal. After withdrawal of AEDs, 21% to 37% of patients with childhood-onset epilepsy experience recurrence of seizures within 2 years [7,8,11-14]. The risk factors for seizure recurrence after AED withdrawal have been investigated [8,11-15]. However, history of status epilepticus as a predictive factor has rarely been mentioned.

Berg et al.[16] used a Markov process to model the course of childhood epilepsy. This method characterizes remissions and recurrences in a more quantitative manner than other methods. It examines the probability of being able in a given state to follow individuals as they change states, and allows for calculation of the net effects. The wavelike pattern might have an important effect on the personal development of patients. However, it might also merely be a consequence of the method. This will have to be confirmed with additional studies on the course of seizure control. Ohta et al.[17] identified in 82 children with cryptogenic focal epilepsy, two independent risk factors for seizure recurrence after discontinuation of AEDs: 5 years or more from start of AED therapy until seizure remission, and age of onset ≥ 6 years. However, their criteria for discontinuing AEDs were ≥ 3 seizure-free years and no abnormal EEGs or tracings, both of which indicate a low seizure recurrence rate (9.8%).

The optimal regimen for discontinuation has been given little attention. Recommendations for tapering off of AEDs have ranged from abrupt discontinuation of therapy to gradual tapering off over a period of 2 years. Tennisonet al.[18] reported that the risk of seizure recurrence during drug

tapering and after discontinuing AEDs in children was not significantly different for tapering off periods of 6 weeks and 9 months.

In the present study, we found no significant differences in the tapering off period between the patients with and without seizure recurrence. The period from the initiation of tapering off to discontinuation of AEDs was longer than in many other studies[7,18]. This is because some of the patients and their parents were anxious about seizure recurrence following discontinuation of AEDs. Therefore, the tapering off period varied from 6 months to 2 years. Data from a large randomized trial[19] showed that tapering off of AEDs after two seizure-free years substantially increases the risk of seizure recurrence 1-2 years after tapering off, but that afterward, the risk parallels that of the group randomly chosen to continue treatment.

Factors that most influence seizure recurrence tend to differ from those that influence remission. Berg and Shinnar[8] demonstrated in their meta-analysis a greater relative risk of seizure recurrence in patients with remote symptomatic seizures than in patients with cryptogenic or idiopathic seizures. Benign rolandic epilepsy responds well to treatment, and relapse is almost unknown when AEDs are stopped[18,20]. However, even though prognosis is worse, approximately 50% of patients with remote symptomatic epilepsy in remission remain seizure-free after AEDs are stopped[8,19,21]. In the present study, after discontinuing AEDs, 3 of 45 (7%) children with benign rolandic epilepsy showed recurrence of seizures and 23 of 66 (35%) with benign rolandic epilepsy did not ($p < 0.001$). This finding suggests that the outcome of benign rolandic epilepsy is excellent; however, some with benign rolandic epilepsy might experience

Table 2. ***Distributions of epilepsy syndromes in individuals with childhood-onset epilepsy***

Epilepsy syndrome	*With relapse (n=45), n (%)*	*Without relapse (n=66), n (%)*	*P-value*
Localization related	**39 (87)**	**49 (74)**	
Idiopathic	10 (22)	28 (42)	N.S.
Rolandic	3	23	
Occipital	7	5	
Symptomatic	11 (24)	5 (8)	0.014
temporal lobe	6	3	
frontal lobe	4	1	
occipital lobe	1	1	
Cryptogenic	18 (40)	17 (26)	N.S.
Generalized	**5 (11)**	**15 (23)**	
Idiopathic	3 (7)	14 (21)	N.S.
childhood absence	1	6	
juvenile myoclonic	0	1	
Generalized tonic-clonic seizures on awakening	2	6	
Other IGE/ unclassified IGE	2	2	
Undetermined whether focal or generalized	**1 (2)**	**2 (3)**	
Total	45	65	

IGE: idiopathic generalized epilepsy; P values from Fisher's exact test; N.S, non-significant

Table 3. ***Risk factors for recurrence following withdrawal of antiepileptic drug therapy in children with epilepsy***

Risk factors	*Odds ratio*	*95% CI*	*P-value*
History of status epilepticus	10.0	1.13-466.8	0.017
Symptomatic focal epilepsy	3.95	1.13-15.6	0.014
Abnormal EEG at withdrawal	2.26	1.02-5.02	0.031

CI: confidence interval. P values from Fisher's exact test.

recurrence of seizures later, which is compatible with an atypical course of rolandic epilepsy[22,23].

A younger age at epilepsy onset is also associated with a higher risk of seizure recurrence after discontinuing AEDs,[21,24] but it appears to be limited to those with remote symptomatic etiology[21]. Younger age at onset is frequently a marker of more severe neurologic impairment. In our study, age at onset was correlated with risk of seizure recurrence after stopping AEDs. Recurrence occurred in 6 (67%) of 9 children who were **< years** old at onset, which was significantly higher than among children aged **< years** at onset.

The risk of seizure recurrence in those with an abnormal EEG before discontinuation of AEDs is significantly higher than in those without,[1,8,18,20,24] but contradictory findings have been reported[25,26]. EEG abnormalities include epileptiform discharges and slowing. In the present study, slowing was associated with a greater risk of recurrence, but epileptiform discharges were not. Slowing on EEG, both generalized background slowing and focal slowing, generally raises concerns about underlying brain dysfunction. In contrast, focal spikes are found primarily in children with benign focal epilepsy, who have a particularly favorable prognosis.

This study was not population-based. Our patients most likely presented more severe varieties of epilepsy. Therefore, the results are not applicable other than in a referral center context. Remission rates after AED withdrawal may be higher in a more representative sample population.

In conclusion, our data indicated that the following are risk factors for seizure recurrence: history of status epilepticus, symptomatic focal epilepsy, and abnormal EEG at the time of AED withdrawal. We suggest that clinicians carefully evaluate the risk factors for seizure recurrence in epileptic children before discontinuation of AEDs after 2-year seizure remission.

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Declaration of Conflicting Interests

The authors declare that they have no conflicts of interest with respect to the authorship or publication of this article.

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