



Clinical Study

Prospective study on the withdrawal and reinstatement of antiepileptic drugs among seizure-free patients in west China



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ABSTRACT

This study explored the relapse rates and risk factors for seizure recurrence after discontinuing antiepileptic drug (AED) therapy among seizure-free patients in west China, and explored whether to reinstate AED immediately after a single seizure after AED withdrawal. Patients with epilepsy who were seizure-free for at least 2 years and decided to gradually stop AED therapy were followed up every 3 months for seizure relapse. Patients who experienced their first seizure after drug withdrawal were divided into two groups according to their willingness to reinstate AED therapy, and were followed up until their second seizure. In the mean 29.35 months of follow-up, 37 patients (37/162, 22.8%) suffered at least one seizure after withdrawal. The cumulative probability of seizure recurrence was 16% at 12 months and 20.2% at 24 months. AED response time >1 year and multiple types of seizure were identified as risk factors for seizure recurrence. Eight patients (8/32, 25%) suffered a second seizure within 1 year after the first whether or not they reinstated AED immediately. There were no significant demographic or clinical differences between patients who reinstated AED therapy and those who did not. The epilepsy recurrence rate after AED withdrawal is relatively low, with a relatively slow tapering process. Patients with long AED response times and/or multiple types of seizures have a higher risk of seizure recurrence. The first seizure after drug withdrawal is not an indication for immediate AED reinstatement, but may be recommended after a second seizure.

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1. Introduction

Epilepsy is one of the most common chronic neurological disorders. About 70 million patients have epilepsy worldwide and 50.4/100,000 new cases occur every year [1]. Epilepsy causes serious physiologic, psychological, and economic burden [2]. Fortunately, approximately 70% of patients with recent-onset epilepsy become seizure-free with reasonable drug therapy [3]. The next consideration is whether these antiepileptic drugs (AED) should be withdrawn once the patient becomes seizure-free. Considering the side effects and huge cost of medication, AED should be withdrawn once they become unnecessary. The main barrier to this is the fear of relapse after discontinuing AED.

In recent decades, many studies have focused on the risk of seizure recurrence after AED withdrawal, which varies from 12% to 67% [4], depending on the research method and population. Studies have also identified some relapse risk factors, including age at seizure onset, type and severity of epilepsy, duration of active epilepsy, period of seizure freedom on AED, multiple AED, abnormal

electroencephalography (EEG) before drug withdrawal, presence of recognised epileptogenic lesions in neuroimaging, and certain epilepsy syndromes, such as juvenile myoclonic epilepsy [5–13]. Furthermore, after AED withdrawal, most patients choose to reinstate therapy (restart AED or increase the dosage) immediately after a seizure occurs, and most achieve seizure control again [14,15]. However, some experts exclude single seizures as relapses: thus, they deem management unnecessary [16]. Additionally, some patients refuse to reinstate AED due to their side effects.

Few studies have focused on AED withdrawal in patients in west China. This study aimed to determine the incidence and risk factors of seizure recurrence after discontinuing AED among seizure-free patients in west China. We also sought to determine whether AED should be reinstated immediately after a single seizure following AED withdrawal.

2. Methods

2.1. Patients

The study population consisted of epilepsy patients from the Department of Neurology at West China Hospital between March

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2006 and June 2011. All patients in the study were candidates for AED withdrawal who were followed up every 3 months until October 2012. A total of 172 patients fulfilled the inclusion and exclusion criteria.

The inclusion criteria were as follows: (1) diagnosis of epilepsy, defined as at least two unprovoked seizures at least 24 hours apart; (2) patients remained seizure-free for at least 24 consecutive months during AED therapy [9,11,17,18]; and (3) patients expressed a desire to gradually discontinue AED therapy and agreed to return for regular follow-up.

The exclusion criteria were as follows: (1) patients with psychogenic seizures or uncertain diagnosis of epilepsy; and (2) patients who underwent epilepsy surgery.

2.2. Methods

All information was recorded on case-record forms by trained extractors. The demographic data and risk factors were collected as follows: sex; age at drug withdrawal; age at seizure onset; period between the start of AED and the last seizure before withdrawal (AED response time); seizure-free period before AED withdrawal; duration of follow-up after AED withdrawal; AED tapering off period (taper period); findings on brain CT scan and/or MRI; EEG before drug withdrawal; seizure type (classified as generalised, partial, or multiple types based on history); number of episodes (frequency multiplied by duration of active seizures); and number of AED administered for long-term seizure control.

The AED doses were slowly tapered off by one-quarter every 3 months in most patients [8]. Those taking one AED were tapered off for at least 6 months and those taking multiple AED were tapered off for 12 months. All patients were followed up every 3 months until the end of the study period. Patients who could not return to the hospital for follow-up were followed-up by telephone.

Patients who experienced their first seizure after AED withdrawal were assigned to one of two groups according to their willingness to reinstitute AED therapy. The patients were again followed up for another 12 months or until their second seizure. All patients who suffered two or more seizures after withdrawal were advised to reinstitute AED therapy immediately.

2.3. Statistics

The Statistical Package for the Social Sciences version 17.0 was used to analyse the data (SPSS, Chicago, IL, USA). Survival analysis was performed to determine seizure recurrence. Survival time was defined as the period between AED withdrawal and seizure recurrence or end of follow-up. The censored value was defined as the first seizure after withdrawal or being seizure-free at the end of follow-up. A survival curve was constructed to describe the recurrence rate after AED withdrawal. A log-rank test was used for univariate analysis and a Cox proportional hazard model was used for multivariate analysis to identify the risk factors for seizure recurrence. A chi-squared test (Fisher's exact test) was used to distinguish the differences in the incidence of second seizures between groups that reinstated AED and those that did not. All statistical tests were two-tailed. Differences between groups were considered significant at $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 172 patients were enrolled from March 2006 to June 2011 in this study. Ten patients (5.8%) were excluded from the analysis because of incomplete follow-up information, meaning we pro-

spectively studied 162 patients. The characteristics of the subjects are shown in Table 1. Most patients were male and only 51 patients had adult onset (>18 years old at onset). The average time of follow-up was more than 2 years (29.35 months), and most seizure-free periods before withdrawal exceeded 3 years (42.33 months). The most common type of seizure was generalised seizures. Abnormal neurological imaging findings included cerebral dysplasia, calcifications, cysts, encephalomalacia, and hippocampal degeneration, whereas abnormal EEG consisted of spiked, sharp, or slow waves. Most patients achieved long-term seizure control with AED monotherapy, but only after more than 1 year of treatment.

3.2. Seizure recurrence

A total of 37 patients (22.8%) experienced at least one seizure after AED withdrawal, with a mean follow-up time of 29.35 months. The details are shown in Table 2. The precipitating factors for seizure included staying up late, drinking wine, missing an AED dose, fever, and drinking coffee. Most patients (73%) chose to reinstitute the AED therapy immediately after their first seizure. A survival curve is presented in Figure 1. Most patients (70.3%) relapsed within 12 months

Table 1
Characteristics of epilepsy patients undergoing antiepileptic drug withdrawal

Characteristic	Number of patients (%) / Mean \pm SD (range)
Patients	162
Male	82 (50.6%)
Age at drug withdrawal, years	24.17 \pm 13.27 (4–79)
Age at seizure onset, years	16.79 \pm 13.20 (1–74)
Adult onset	51 (31.5%)
AED response time, months	18.41 \pm 26.61 (0–138)
AED response time >1 year	92 (56.8%)
Seizure-free period, months	42.33 \pm 17.92 (24–168)
Seizure-free period <3 years	26 (16%)
Duration of follow-up, months	29.35 \pm 13.10 (15–79)
Taper period, months	
With one AED	10.65 \pm 4.93 (4–30)
With multiple AED	16.71 \pm 6.60 (8–34)
Seizure type	
Generalised	105 (64.8%)
Partial	33 (20.4%)
Multiple types	24 (14.8%)
Number of AED	
One	111 (67.3%)
Multiple	55 (32.7%)
Abnormal findings on neuroimaging	20 (12.3%)
Abnormal EEG before drug withdrawal	30 (18.5%)

AED = antiepileptic drug, EEG = electroencephalography, SD = standard deviation.

Table 2
Characteristics of epilepsy patients who relapsed after antiepileptic drug withdrawal

	Patients, n	Percent
Patients	37	100.0
Male	17	45.9
Adult onset	14	37.8
AED response time >1 year	20	54.1
Seizure-free period <3 year	5	13.5
Multiple AED	17	45.9
Multiple types of seizure	9	24.3
Abnormal findings in neuroimaging	5	13.5
Abnormal EEG before withdrawal	6	16.2
With precipitating factor	13	35.1
AED reinstatement	27	73.0

AED = antiepileptic drug, EEG = electroencephalography.

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