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Risk of seizure relapse after antiepileptic drug withdrawal in adult patients with focal epilepsy

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ABSTRACT

Objective: The objective of this study was to estimate the risk of a seizure relapse and the high-risk period of recurrence after antiepileptic drug (AED) withdrawal and to determine the predictive factors for a seizure relapse in adult patients with focal epilepsy who were seizure-free for more than 2 years.
Methods: Using the Wenzhou Epilepsy Follow-Up Registry Database, 200 adult patients with focal epilepsy were recruited, who were undergoing follow-up, met the inclusion criteria of this study, were seizure-free for more than 2 years, began withdrawing between June 2003 and June 2014, and were followed up prospectively for at least 1 year or until a seizure relapse. The risk of recurrence and the time to seizure relapse were analyzed by the Kaplan–Meier method, and the predictive factors were identified by the Cox proportional hazard regression model.
Result: A total of 99 patients had an unprovoked relapse during the follow-up period. The relapse rate was 49.5%, and each year, the recurrence probability of 12, 24, 36, 48, 60, 72, and 84 months after AED withdrawal was 24.0%, 20.4%, 8.3%, 2.7%, 4.6%, 0.97%, and 0.98%, respectively. The two independent risk factors for recurrence after withdrawal in adult patients with focal epilepsy were a longer duration of active epilepsy and a shorter seizure-free period before withdrawal.
Conclusion: The high-risk period of a seizure relapse in adult patients with focal epilepsy is the first 2 years after withdrawal, and beyond 5 years after withdrawal, seizures rarely relapse (relapse rate < 1%). A seizure-free period for less than 4 years before withdrawal is a predictive factor of risk for seizure recurrence after AED withdrawal in adult patients with focal epilepsy.

1. Introduction

Drug therapy is still the main treatment of epilepsy at present [1]. With antiepileptic drugs (AEDs), about 70% of patients with newly diagnosed epilepsy become seizure-free [2]. For patients who attain long-term remission under AED treatment, the most important concern is "when is it suitable to discontinue AEDs and does it relapse after withdrawal?" This issue remains difficult for clinicians, especially for adult neurologists, because the recurrence of seizures in adult patients with epilepsy causes more serious social consequences, such as unemployment, losing driver's license, injury, and even death.

Although discontinuing AEDs increases the risk of recurrence, it may improve behavior and cognitive function [3–5] and also reduces the financial burden of the cost of medication. Therefore, it is essential for clinicians to assess the relapse risk and predictive factors for seizure relapse after withdrawal.

In the past decades, numerous studies on AED withdrawal have estimated the relapse risk. The relapse risk after withdrawal in patients who were seizure-free for at least 2 years fluctuated from 12% to 67% [6–8]. In addition, many factors have been implicated in previous studies to affect the rate of seizure recurrence. However, the risk factors associated with a seizure relapse are yet to be fully identified and still remain controversial.

As the published research on AED withdrawal have relied mainly on the heterogeneous study population, the conclusions of these heterogeneous outcomes are challenging to translate to specific types of patients in clinical practice. In addition, only a few studies are specifically related to the issue of AED withdrawal in adult patients [3,9,10], and no research focused attention on the withdrawal prognosis of adult patients with focal epilepsy.

Therefore, the aim of the present study was to estimate the relapse risk and the high-risk period of recurrence after withdrawal as well as to determine the predictive factors for seizure relapse in adult patients with focal epilepsy who were seizure-free for at least 2 years.

Abbreviations: AED, antiepileptic drug; WEFURD, Wenzhou Epilepsy Follow-Up Registry Database; ILAE, International League Against Epilepsy; EEG, electroencephalography.

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2. Materials and methods

2.1. Recruitment and observation time setting

This was a prospective observational study conducted from June 2003 to June 2014. The patients who were undergoing regular and long-term follow-up and satisfied the inclusion criteria were recruited from the registration database—Wenzhou Epilepsy Follow-Up Registry Database (WEFURD). The details of WEFURD were introduced in a previous publication [11]. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, China, and written informed consent was not required. The deadline of observation was June 30, 2015.

2.2. Patients

The target population was recruited from the specialized epilepsy outpatient clinic of the First Affiliated Hospital of Wenzhou Medical University. The inclusion criteria were as follows: (1) diagnosis of focal epilepsy according to the 1989 classification of the International League Against Epilepsy (ILAE) [12]; (2) diagnosed age ≥ 16 years; (3) patients who had begun to discontinue AEDs after a period of at least 2 years' remission; (4) at least one-time cerebral computed tomography/magnetic resonance imaging (CT/MRI) and electroencephalography (EEG) or video-EEG (VEEG) performed; and (5) a period of follow-up of at least 1 year (or until seizure relapse). The following were exclusion criteria: (1) Lennox–Gastaut syndrome and childhood or juvenile onset idiopathic partial epilepsy; (2) poor drug adherence (the actual taken medicine dose ≤80% of the prescription dose); (3) serious dysfunction of the liver, kidney, heart, and lung; (4) history of epilepsy surgery; and (5) remission obtained by neuromodulation surgery such as vagus nerve stimulation or by Chinese herbal medicine treatment.

2.3. Withdrawal process

When patients achieved seizure remission for more than 2 years, they were informed of the potential benefits and risks of stopping the medicine. But the final timing of AED withdrawal was decided by the patient's willingness with the advice of physicians. Additionally, the tapering period of withdrawal (the period between the beginning and the end of withdrawal) was at least 6 months. However, a few patients had a rapid tapering period (less than 6 months), which was defined as "rapid withdrawal", while a few others were not completely withdrawn until the deadline of observation and remained in a prolonged partial withdrawal status.

2.4. Follow-up

The candidates for this of this study in WEFURD were interviewed on-site or by phone at least once every 3–6 months before the start of withdrawal. After withdrawal, follow-up visits were scheduled every 3 months during the first year and every 6–12 months thereafter.

2.5. Measurements

(1) The main outcome end points were as follows: seizure relapse after withdrawal and time to the first seizure relapse after withdrawal.
(2) The potential outcome risk factors were as follows: gender, age at epilepsy onset, family history of epilepsy, history of febrile convulsion, perinatal history, history of status epilepticus, types of seizures (partial and/or secondarily generalized seizures) and number, seizure frequency before seizure control, results of MRI or CT examination, etiology, neurological and psychiatric findings, duration of active epilepsy, seizure-free period before withdrawal, initial treatment response, AED at withdrawal (monotherapy or polytherapy), previous unsuccessful withdrawal attempt, number of ineffective drugs used, tapering period, and EEG/VEEG findings at first diagnosis and before AED withdrawal.

2.6. Definitions

The diagnosis of epilepsy was defined as the occurrence of two or more unprovoked seizures at least 24 h apart [13]. The diagnosis of focal epilepsy was based on a patient's ictal clinical focal semiology (witnessed by doctors, description by patients or their family, or by video records). Furthermore, the type of seizure was classified as focal (simple/complex) and/or secondarily generalized according to the 1981 ILAE criteria [14]. Epilepsies were classified according to their etiology as cryptogenic (localization-related epilepsy without definitive etiological pathology findings) or symptomatic focal epilepsies. Recently, "cryptogenic" and "symptomatic" were replaced with "unknown" and "structural/metabolic", following the 2010 ILAE criteria [15].

The "partial withdrawal status" was defined as the status in which patients tapered off AEDs gradually to stop their medicine as the ultimate goal but were not completely withdrawn and remained in the prolonged low-dose status (low-dose status was established as a reduction of at least 75% of the maximum effective dose). The definition of "partial withdrawal status" was taken from a published exploratory prospective randomized study that showed that leaving seizure-free patients on a low AED dose (a reduction of at least 50% of the initial dose) did not reduce the risk for seizure recurrence compared with complete withdrawal [16]. The definition of nonseizure was according to the patients or family report that there had not been any type of epileptic seizure. A seizure relapse after withdrawal was defined as the recurrence of seizures without any provocations after withdrawal. The duration of active epilepsy was defined as the period between the first and last seizures. The seizure frequency before seizure control was defined as the average seizure frequency between the first and last seizures (the total number of seizures/the duration of active epilepsy). The initial treatment response was defined as the period between the start of AED treatment and the last seizure before the seizure were controlled and coded ≤6 months or >6 months according to the publication by Brodie et al. [17].

The EEG/VEEG abnormalities referred to epileptiform discharges whereas "normal" indicates absence of epileptiform activity. Electroencephalography was performed according to the international 10–20 electrode placement system, recording at least 30 min. A Nicolet digital electroencephalograph machine was used for VEEG, recording at least 120 min.

2.7. Statistical analysis

The SPSS version 17.0 software package (SPSS) was used for statistical analysis. The calculation of the risk of recurrence and the time to seizure relapse were analyzed by the Kaplan–Meier method. The statistically significant possible prognostic factors were first evaluated by the chi-square test (or Fisher exact test). Then, the factors found to be significant in the chi-square test and those thought to be clinically relevant were both investigated by the Cox proportional hazard regression model (uni/multivariate analyses) to obtain a hazard ratio (HR) and a 95% confidence interval (95% CI). The final independent risk factors were identified by multivariate analyses. Additionally, an unprovoked seizure relapse was defined as an "event" in both the Kaplan–Meier method and Cox regression analysis. A P value of less than 0.05 was considered to be statistically significant.