Factors predictive of late remission in a cohort of Chinese patients with newly diagnosed epilepsy

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ABSTRACT

Purpose: Limited data have focused on predictive factors of late remission in patients with newly diagnosed epilepsy. We are aiming to identify prognostic predictors of late remission in a prospective cohort of Chinese patients.
Methods: Patients with newly diagnosed epilepsy were included from 2009 to September 2012 at a tertiary hospital, with follow-up of at least two years. Early remission was defined by seizure free either immediately or within six months of treatment initiation, late remission was defined by seizure free achieved after more than six months. All analyses were performed with SPSS 13.0 software.
Results: A total of 223 patients were included, and followed for an average of 43 months. 115 patients (51.6%) achieved early remission and 39 patients (17.5%) achieved late remission. Multivariable logistic regression analysis demonstrated more than 3 seizures prior to treatment (OR = 3.12, 95% CI 1.39–7.04, $p = 0.006$) and multiple seizure types (OR = 2.49, 95% CI 1.02-6.11, $p = 0.046$) may predict late remission. However, nonadherence was not significantly associated with late remission.
Conclusion: Patients with a high frequency of seizures prior to treatment or multiple seizure types may achieve late remission. Particular consideration should be given to these patients.

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1. Introduction

Epilepsy is one of the most common neurological conditions, with more than 50 million people affected worldwide [1]. Studies in well-defined populations with newly diagnosed epilepsy have shown the majority of patients achieve remission at some time after the onset of the disease, and about one-third of patients have recurrent seizures despite optimal therapy with available antiepileptic drugs (AED) [2–4]. Four different patterns of clinical outcome have been identified: early remission, late remission, relapsing-remitting course, and never remission [5,6]. To formulate rational treatment plans, it is important to understand the different patterns of response to AED treatment and associated predictors.

Several factors was found to be negatively associated with early remission in patients with newly diagnosed epilepsy, such as early age at seizure onset, etiology, long duration of epilepsy, and electroencephalography (EEG) abnormality [7–9]. However, limited data were available on prognostic indicators of late remission, particularly in Chinese, necessitating studies on this field. Moreover, there were no studies carried out to assess the association between patients' compliance and late remission. Therefore, we are aiming to explore the patterns of treatment outcome and to identify factors predictive of late remission in a prospective cohort of Chinese patients with newly diagnosed epilepsy.

2. Materials and methods

2.1. Population

The prospective, observational study was performed at a tertiary hospital which served a population of approximately 350,0000 each year. Newly diagnosed patients were included from 2009 to September 2012 when a definite diagnosis of epilepsy was made according to the International League against Epilepsy (ILAE) [10] (i.e., two or more unprovoked seizures at least 24 h apart, or if they had a definite epileptic focus on brain MRI or epileptiform discharges on EEG if they had suffered only one epileptic seizure

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with confirmation by a neurologist). Patients were excluded if they (1) refused treatment with AEDs, (2) were taking more than one AED, (3) had received epilepsy surgery during the follow-up, (4) had severe hepatic or renal diseases. The study was approved by the Second Affiliated hospital of Zhejiang University School of Medicine Ethics Committee.

For each eligible case, the following data were collected at the first visit: patient demographics, age at seizure onset, pretreatment duration, seizure frequency before starting AED, seizure types, past history (i.e., head trauma, tumor, stroke, encephalitis), family history of epilepsy, febrile seizures, EEG and MRI findings. Monotherapy was recommended when starting treatment, and all the drug choice and schedule were done by standard. Patients were evaluated at 4 weeks after treatment initiation and then at 6-month intervals thereafter. At each visit, seizure frequency, choice of AEDs, and response to AEDs were routinely recorded. Patients were followed up until the end of June 2015, i.e., for at least two years. Multiple seizure types were defined as two or more seizure types, which included simple partial seizure, complex partial seizure, tonic-clonic seizures, etc. Adherence was examined by the validated Chinese version of the MMAS-4 (4-item Morisky Medication Adherence Scale) [11]. Adherence was defined as a "no" answer to every question, and nonadherence was defined as a "yes" answer to one or more questions.

2.2. Definition

Patterns of seizure outcome over time were classified according to pre-selected definition. The timing point was set in accordance to Brodie's study [6]. Remission was considered as a period of uninterrupted seizure free lasting one year or longer at any time and categorized into early and late remissions. Early remission was achieved either immediately or within six months of treatment initiation, as opposed to late remission, which was achieved after more than six months of treatment. Relapsing-remitting course described the occurrence of repeated seizures after remission achieved. Never remission was defined as never enter one-year remission during the follow-up. Sustained remission was defined as seizure free until the end of follow-up. According to the definition proposed by the ILAE, drug resistant epilepsy (DRE) was defined as the failure of two well-tolerated and appropriately chosen AEDs, whether as monotherapies or in combination, to achieve sustained seizure free for either one year or for a period equal to three times of the pre-intervention inter- seizure time, whichever was longer.

2.3. Data analyses

The continuous data were described as mean (range). Among those patients who achieved early and late remission, each predictive factor was tested with two-tailed chi-square or Fisher's exact tests. Factors with significantly different distribution were further assessed by multivariate logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were calculated. The p value of < 0.05 was considered as statistically significant. Additionally, a time-dependent analysis on cumulative remission was calculated with the Kaplan-Meier method. All analyses were performed with SPSS 13.0 software.

3. Results

3.1. Study characteristic

A total of 250 patients were diagnosed with epilepsy and none had previously received AEDs. 27 patients (10.8%) were excluded from analysis because of lack of follow-up information. Finally,

Table 1
General characteristics of the sample.

Variable	Number of patients (N = 223)	Percentage (%)
Gender		
Male	112	50.2
Female	111	49.8
Occupation		
Students	105	47.1
Unemployment	30	13.5
Employment	88	39.5
Residence		
Urban	115	51.6
Rural	108	48.4
Education		
Illiteracy or primary school	35	15.7
Secondary school or above	188	84.3
Age at onset		
≤16	101	45.3
>16	122	54.7
Seizure type		
Focal seizure	189	84.8
Generalized seizure	21	9.4
Unclassified seizure	13	5.8
Multiple seizure types		
No	163	73.1
Yes	60	26.9
Febrile seizure		
Negative	208	93.3
Positive	15	6.7
Past history		
Negative	162	72.6
Brain trauma	33	14.8
Intracranial infection	11	4.9
Others, e.g. stroke	17	7.6
Family history		
Negative	216	96.9
Positive	7	3.1
Pretreatment duration		
≤ 12 months	152	68.2
> 12 months	71	31.8
EEG at diagnosis		
Negative	69	30.9
Slow wave	16	7.2
Epileptiform discharge	131	58.7
NA	7	3.1
MRI findings		
Normal	153	68.6
Abnormal	58	26.0
NA	12	5.4

NA not available

outcomes were known for the remaining 223 patients. The median (range) age at referral was 28 (8–88) years, the median (range) age at the onset of epilepsy was 23 (2–85) years, and the median (range) duration of the follow-up was 43 (26–80) months. The general characteristics of the sample was shown in Table 1.

3.2. Seizure outcome

As shown in Fig. 1, of 223 patients with newly diagnosed epilepsy, 154 patients (69.1%) entered one year or longer seizure free: 115 patients (51.6%) achieved early remission and 39 patients (17.5%) achieved late remission. Of these, 96 (43.0%) and 32 patients (14.3%), respectively, were in sustained remission at the last follow-up. The remaining 26 (11.7%) patients relapsed, indicating a remitting-relapsing course of epilepsy. Besides, 69 (30.9%) patients never experienced a one-year remission during the AED therapy. Among them, 44 (19.7%) patients failed to achieve remission after using at least two AEDs and were thus defined as having DRE. The cumulative time-dependent probability of remission was performed using Kaplan-Meier method, which was seen in Fig. 2. The median period of time needed to achieve remission was 24.8 months (range 0–74 months).