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Clinical Study

Initial response to antiepileptic drugs in patients with newly diagnosed epilepsy

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ABSTRACT

This study aimed to identify factors predicting the response to antiepileptic drugs in patients with newly diagnosed epilepsy. We prospectively studied 176 patients with newly diagnosed epilepsy. Patients were included if they had a history of two or more clinically definite unprovoked seizures, or had a definite epileptic focus on MRI or epileptiform discharges on electroencephalography if they had suffered only one seizure. The primary endpoint was seizure freedom during the initial 6 months of antiepileptic drug treatment. The secondary endpoint was the time to the first seizure during the maintenance period of antiepileptic drug treatment. A total of 100 patients were included, and seizure freedom for 6 months was achieved in 73 patients. The response to antiepileptic drugs was significantly lower in patients with early age at seizure onset ($\leqslant$16 *versus* >16 years old, odds ratio = 4; 95% confidence interval [CI] 1.5–12.9; relative risk = 1.4; 95% CI 1.1–1.8). In addition, the time to the first seizure during the maintenance period was significantly earlier in patients with age at seizure onset $\leqslant$16 years compared with those with age at seizure onset >16 years on the Kaplan–Meier survival analysis ($p = 0.011$). Early age at seizure onset is an important factor influencing the response to antiepileptic drugs in patients with newly diagnosed epilepsy.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, and affects at least 50 million people worldwide [1]. Antiepileptic drugs (AED) are the treatment of choice for most patients with epilepsy [2]. Approximately 47% of patients with epilepsy will respond to the first AED, whereas only about 4% will have significant improvement with further AED trials [3]. Thus, identifying clinical factors associated with the initial response to AED is important. Studies investigating the clinical factors predicting response to AED found that early onset of epilepsy, higher frequency of seizure, multiple seizure types, prolonged disease duration, symptomatic etiology (for instance, due to hippocampal sclerosis), family history of epilepsy, and psychiatric morbidity appeared to be associated with a poor response to AED [4–16]. However, these studies were often retrospectively designed [9,11], selected patients with a diagnosis of epilepsy that had been established for variable periods of time [5,11], or included only adults [3,5,9,11,12] or children [4,8,10,13–16].

In 2006 and 2013, the International League Against Epilepsy (ILAE) published papers about the long-term efficacy and effectiveness of AED as initial monotherapy for patients with newly diagnosed or untreated epilepsy [17,18]. The studies recommended efficacy and effectiveness of AED as a primary outcome variable based on a minimum of 6 months of seizure freedom (efficacy) and retention of AED for a period of $\geqslant$48 weeks (effectiveness) [17,18]. Many previous studies used seizure freedom for 6 months as a primary outcome to evaluate AED efficacy [19–21]. In addition, a previous study demonstrated that patients who were seizure-free for 6 months had a 90% chance of being seizure-free for 12 months, and that the response to an AED at 6 months was an excellent predictor for the response at 12 months [22]. Other studies have also reported that patients who have an early response to an AED have a better prognosis [4,8], and patients who do not respond early to an AED will usually develop intractable epilepsy [23]. Thus, studying the initial response to AED for 6 months is

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useful not only for clinical practice but also for patient counseling. These findings can be explained by two assumptions [14–16]. The first is an epileptic disposition that makes epilepsy refractory to AED both immediately after onset and later [14–16]. The theory of intrinsic disease severity is that neurobiological factors that confer increased disease severity lead to drug intractability, and the occurrence of frequent seizures at disease onset is an important factor signaling increased severity [24]. The second assumption is that persistence of seizures makes seizures worse, first proposed by Gowers in 1881 [14–16]. Experimental studies in animals provided additional support that it was possible to cause increased susceptibility to seizures by stimulating brain pathways and inducing subclinical epileptic activity or overt clinical seizures [25].

We conducted a prospective study in patients with newly diagnosed epilepsy, involving both children and adults, and used the primary outcome that the ILAE recommended. The aim of this study was to indentify clinical factors associated with the initial response to AED for 6 months in patients with newly diagnosed epilepsy.

2. Methods

This study was approved by the Institutional Review Board at our institution. This prospective, observational study was performed at a single tertiary hospital which serves a population of approximately 400,000. Patients were included if they had a history of two or more clinically definite unprovoked epileptic seizures, or if they had a definite epileptic focus on brain MRI or epileptiform discharges on electroencephalography (EEG) if they had suffered only one epileptic seizure. Patients were excluded if they (1) refused treatment with AED, (2) were taking more than one AED, (3) were having seizures that were too frequent to count, such as in epileptic encephalopathy, or (4) had a prolonged duration (more than 24 months) from the first seizure onset to starting AED (pretreatment duration).

Information recorded at the time of entry into the study included patient demographics, pretreatment duration, total seizure frequency before starting AED (pretreatment seizure frequency), seizure frequency for the previous 6 months before starting AED (seizure density), age at seizure onset, and EEG and MRI findings. We classified seizures and epilepsy using the current ILAE classification [26]. The choice of AED, period of titration, and initial maintenance dose were decided by the treating clinician, and the minimum effective dose of the drug was recommended.

The primary endpoint for this study was seizure freedom for the initial 6 months of AED treatment. Patients were considered responders if they had not had any seizures for 6 months, and we did not include seizures that occurred during the titration period of the AED. We also excluded the seizures that occurred during sleep deprivation or when the patient was not taking an AED. The secondary endpoint was the time to the first seizure during the maintenance period of AED. We divided independent variables into three categories. First, factors that were thought to be associated with intrinsic disease severity such as pretreatment duration, pretreatment seizure frequency, seizure density and age at seizure onset were considered. Second, the electroclinical factors such as epileptiform discharges on EEG, presence of structural lesions on MRI which were possibly of epileptogenic pathology, classification of seizures, and epilepsy classification were considered. Last, the types of AED, according to their modes of action, were considered. We divided AED into three groups: (1) voltage-gated sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine, and lamotrigine), (2) multiple mechanisms of actions (valproic acid, topiramate, zonisamide, and phenobarbital), and (3) binding to synaptic vesicle protein 2A (levetiracetam).

We analyzed clinical variables using Fisher's exact test or the chi-squared test for categorical variables, and Student's *t*-test or the Mann–Whitney U test for numerical variables. We performed multiple logistic regression analyses, and calculated odds ratios (OR) with 95% confidence intervals (CI) of having seizures. For multivariate analyses, we dichotomized age at seizure onset as >16 years old or ⩽16 years old. The time to the first seizure during the maintenance period of AED treatment in patients with age at seizure onset >16 years and ⩽16 years was analyzed using Kaplan–Meier survival analysis. All statistical tests were performed using MedCalc (MedCalc Software, Ostend, Belgium). A p value <0.05 was considered significant.

3. Results

We identified 176 patients with newly diagnosed epilepsy between March 2010 and October 2012. Of the 176 patients, 100 patients (50 males and 50 females) met the inclusion criteria for this study. Of the 100 patients, 73 patients were responders for 6 months after initiation of AED, 56 patients showed epileptiform discharges on EEG, and 18 patients had structural lesions on MRI that were of possible epileptogenic pathology. Eighty-two patients had focal seizures, 17 patients had generalized seizures, and one patient had unknown seizures. Six patients had an electroclinical syndrome of childhood onset (five patients with benign epilepsy with centrotemporal spikes and one patient with childhood absence epilepsy), and 16 patients had adolescence-adult onset (two patients with juvenile absence epilepsy, seven patients with juvenile myoclonic epilepsy, and seven patients with epilepsy with generalized tonic–clonic seizures alone). Whereas one patient had epilepsy of distinctive constellations (medial temporal lobe epilepsy with hippocampal sclerosis), 14 patients had epilepsy attributed to structural-metabolic causes (three patients with malformations of cortical development, one patient with a tumor, two patients with infection, three patients with stroke, and five patients with other lesions), and 63 patients had epilepsy of unknown cause. Sixty-five patients took voltage-gated sodium channel blocker AED (36 took oxcarbazepine, 29 took lamotrigine), 17 patients took AED with multiple mechanisms of action (14 took valproic acid, one took topiramate, and two took phenobarbital), and 18 patients took an AED binding to synaptic vesicle protein 2A (all levetiracetam).

The median age at seizure onset was 16 years (95% CI 13.7–19.3, range 1–77). The median pretreatment duration was 2.5 months (95% CI 1–4.3, range 1–24). The median pretreatment seizure frequency was two (95% CI 2–3, range 1–24), and the median seizure density was also two (95% CI 2–2, range 1–15). The age at seizure onset in patients who responded was significantly older than that of non-responders (18 years *versus* 10 years, $p = 0.0004$ by Mann–Whitney U test; Fig. 1). However, there were no significant differences between responder and non-responder patients for pretreatment duration (3 months *versus* 2 months, $p = 0.6394$), pretreatment seizure frequency (2 *versus* 2, $p = 0.4715$) or seizure density (2 *versus* 2, $p = 0.3025$). A multiple logistic regression analysis showed that older age at seizure onset (>16 years old) was the only independently significant variable for predicting response (OR 4, 95% CI 1.5–12.9; relative risk 1.4, 95% CI 1.1–1.8) (Table 1). In addition, the time to the first seizure during the AED treatment maintenance period was significantly earlier among patients with seizure onset at ⩽16 years old compared with those with seizure onset at >16 years old on the Kaplan–Meier survival analysis ($p = 0.011$; Fig. 2). However, there was no significant difference in types of AED, epileptiform discharges on EEG, structural lesions on MRI, or classification of seizures and epilepsy between responder and non-responder patients.