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Presence of epileptiform discharges on initial EEGs are associated with failure of retention on first antiepileptic drug in newly diagnosed cryptogenic partial epilepsy: A 2-year observational study

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ABSTRACT

Objectives: Approximately two-thirds of the patients with newly diagnosed partial epilepsy remained on their first antiepileptic drug (AED) for 2 years in clinical practice. We aimed to analyze retention on the first AED for 2 years in newly diagnosed cryptogenic partial epilepsy patients in clinical practice and whether the presence of epileptiform discharges on the initial EEG was a predictor of the failure of retention on the first AED.

Methods: For the purpose of this study, we retrospectively reviewed epilepsy database. On the Epilepsy Database, we found 495 newly diagnosed epilepsy patients who had been followed up for at least 2 years. Of these 495 newly diagnosed epilepsy patients, 172 patients had cryptogenic partial epilepsy. The outcome of this study was the retention rate for the first AED for 2 years. In addition, we analyzed the retention on first AED according to the presence or absence of epileptiform discharges on the initial EEG using Kaplan–Meier survival analysis.

Results: Overall, retention rate on the first AED for 2 years was 51%. The main lesion of retention failure was a lack of tolerance. The presence of epileptiform discharges on the initial EEGs was significantly related to the failure of retention on the first AED ($p = 0.003$).

Conclusions: In newly diagnosed cryptogenic partial epilepsy, overall retention on the first AED was not significantly different from that in newly diagnosed partial epilepsy. In clinical practice, epileptiform discharges on the initial EEG could predict the failure of retention on the first AED for 2 years.

1. Introduction

Except for a few symptomatic partial epilepsy patients with well-defined lesions, the mainstream of treatment of epilepsy is still antiepileptic drugs (AED) that would control about two-thirds of newly diagnosed epilepsy patients.[1] Randomized controlled trials (RCTs) show that AEDs are efficacious for chronic intractable epilepsy[2–8] as well as for newly diagnosed epilepsy patients.[9–11] However, a direct translation of the results of double-blind RCTs or systemic reviews based on RCTs into daily clinical practice is limited by several factors; double-blind RCTs are designed with fixed doses, a strict primary endpoint reflecting efficacy rather than effectiveness of AEDs, or a relatively shorter follow-up period than clinical practice.[12] In daily clinical practice, not only efficacy but also tolerance of AEDs is very important for treatment of epileptic patients. A recent guideline from ILAE suggests that retention on a certain AED for 48 weeks is a reliable primary endpoint to assess the effectiveness of an AED encompassing both AED efficacy and tolerance.[11]

The response to AED or the prognosis of epilepsy is different between the etiologies of epilepsy.[13] Symptomatic epilepsy is more difficult to control and needs higher doses of AEDs than idiopathic epilepsy. Cryptogenic partial epilepsy is a syndrome that is presumed to be symptomatic but may have unknown etiology in a specific patient; it has neither a definite cause of epilepsy nor an abnormality on MRI. Although cryptogenic partial epilepsy is a common type of partial epilepsy and a more

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homogeneous condition than partial epilepsy as a whole, the response to the first AED in cryptogenic partial epilepsy is seldom known.

We aimed to analyze the retention rate of the first AED for 2 years in newly diagnosed patients with cryptogenic partial epilepsy and whether the presence of epileptiform discharges on initial EEG was associated with the failure of retention on the first AED.

2. Materials and methods

2.1. Subjects

The Institutional Research Board approved this study. All patients were informed the purpose of the study and agreed to a consent form. We registered epilepsy patients from four major regional epilepsy centers in Busan-Kyungnam area, Korea serving a population of approximately 4.5 millions and we have registered 1552 epilepsy patients since July 2006. In the epilepsy center participated for this study, it is not so rare to take care newly diagnosed epilepsy patients that this study is more "population-based" than other European country. The inclusion criteria for this study were newly diagnosed cryptogenic partial epilepsy patients who were regularly taking first AED since the onset of epilepsy for at least 2 years. We excluded the patients who had poor compliance with AEDs, an unreliable medical record or provoked seizures. All of the patients were more than 13 years old.

2.2. Clinical data

We defined newly diagnosed epilepsy as an occurrence of at least two unprovoked seizures separated by at least 24 h and the last seizure should occur within 3 months before diagnosis. None of the patients had been previously exposed to AEDs. Cryptogenic partial epilepsy was diagnosed if the patients had either a partial seizure or secondarily generalized seizure, and did not have a definite cause of epilepsy or abnormality on MRI.

We retrospectively collected the clinical data with a standardized questionnaire when the patients were registered. As none of the patients in this study had significant medical or surgical histories before the onset of epilepsy and abnormal MRI findings, we paid special attention to the initial EEG findings. The definition of the initial EEG was the EEG recorded at the time of diagnosing cryptogenic partial epilepsy. We performed all of the initial EEGs as soon as possible when the patients attended the epilepsy clinic with an index seizure that marked the diagnosis of epilepsy. Majority of the patients commenced on AED after their initial EEG, whereas some of them started AED before initial EEG. All of the initial EEGs were obtained by the international 10–20 system and were recorded for at least 30 min. The standard procedure of initial EEG included the provocation methods such as hyperventilation and photic stimulation as well as recording during sleep. The initial EEGs were interpreted by a qualified epileptologist paying special attention to the possibility of artifacts or normal variations. Epileptiform discharges were present when, (1) being distinguished from background activity, (2) being surface negative discharge, (3) having after-coming slow wave, (4) having electrical field to adjacent electrodes, and (5) having characteristic steep ascending and descending limbs.[14] We divided the patients into groups based on the presence or absence of epileptiform discharges on their initial EEG regardless of sleep or awakening. We did not consider non-specific abnormalities on the EEG, such as focal slowing.

The primary endpoint for this study was retention on the first AED for 2 years. For the patient whom the authors had to switch to another AED because of lack of efficacy or tolerability of a certain AED, we recorded the time (in weeks since the start of the AED) of failing retention of the first AED. We analyzed the retention on the first AED with and without epileptiform discharges on the initial EEG. All of the patients were followed up for at least 2 years after the onset of epilepsy.

2.3. Statistical analysis

The retention on the first AED for 2 years was expressed as a survival curve at each time point in weeks. The retention on the first AED with and without epileptiform discharges on the EEG was analyzed using Kaplan–Meier survival analysis. We used the package of Medcalc Ver 9.5. For all calculations, the significance level was taken as $p < 0.05$.

3. Results

We found 495 epilepsy patients who were newly diagnosed on the epilepsy database and had been followed up for at least 2 years after the onset of epilepsy. Of the 495 epilepsy patients, 389 patients had partial epilepsy and of these 389 partial epilepsy patients, 172 patients had cryptogenic partial epilepsy and 217 patients had symptomatic partial epilepsy. The median age of the 172 cryptogenic partial epilepsy patients was 26 years (range, 15–52 years). Ninety-seven patients were male. The median onset of the epilepsy was 24 years (range, 13–49 years). On the initial EEG, epileptiform discharges were present in 97 patients, whereas 75 patients had normal or non-specific findings such as focal slowing. The first AEDs used were as follows: carbamazepine in 80 patients, lamotrigine in 16 patients, oxcarbazepine in 25 patients, phenytoin in 15 patients, topiramate in 15 patients and valproate in 21 patients.

Of the 172 cryptogenic partial epilepsy patients, 51% (88/172) were still on the first AED for 95 weeks, whereas 84 patients were switched to other AEDs (Fig. 1). Of the 84 patients who failed on retention, 29 patients were due to a lack of efficacy and 55 patients were due to a lack of tolerance. Of the 55 patients who could not tolerate the first AED, 31 patients had idiosyncratic reactions to the AEDs and 24 patients suffered from dose-related adverse events. When we analyzed the retention between older AEDs (carbamazepine, phenytoin and valproate) and newer AEDs (lamotrigine, oxcarbazepine and topiramate), there was a tendency that the newer AEDs were more likely to succeed in retention, however this was not quite statistically significant ($p = 0.06$).

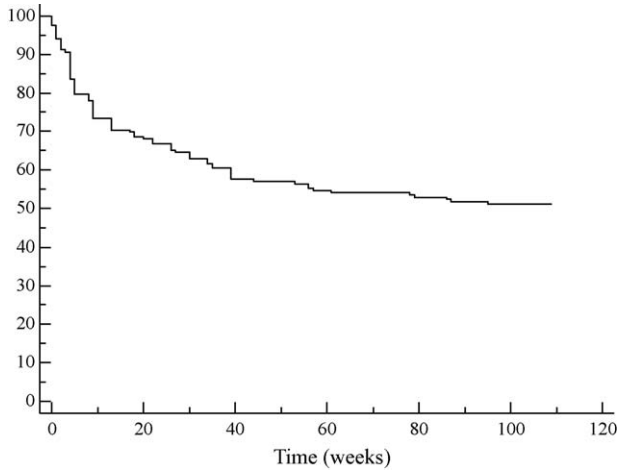

Fig. 1. Retention on the first AED for 2 years in newly diagnosed patients with cryptogenic partial epilepsy. Of the 172 patients with cryptogenic partial epilepsy, 51% (88/172) were still on the first AED at 95 weeks, whereas 84 patients had switched to other AEDs.

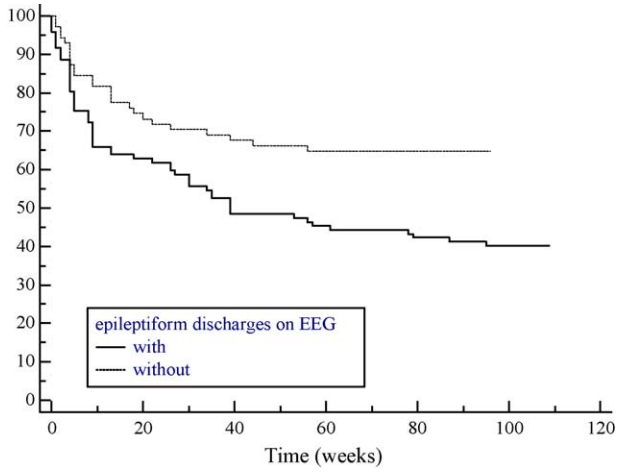

Fig. 2. Retention on the first AED was significantly different between patients with the presence and absence of epileptiform discharges on the initial EEG. The presence of epileptiform discharges predicted the failure of retention on the first AED in newly diagnosed patients with cryptogenic partial epilepsy (Kaplan–Meier survival analysis, $p = 0.003$).

The presence of epileptiform discharges on the initial EEG was significantly associated with the failure of retention on the first AED for 2 years (Kaplan–Meier survival analysis, $p = 0.003$, Fig. 2). The patients having epileptiform discharges showed poor retention on the first AED from a very early phase of the treatment, and this poor retention slowly progressed and reached a retention rate of 40% at 95 weeks. The patients having normal or non-specific focal slowing on their initial EEG revealed that the failure of retention slowly progressed until 56 weeks (65% retention at 56 weeks) and none of the patients switched to other AEDS after 56 weeks.

4. Discussion

A well-designed double-blind RCT is critical to assess the efficacy of a certain AED.[11] The application of results from double-blind RCTs to daily clinical practice is problematic as the follow-up is much longer, doses are more flexible and the goal of the treatment is the effectiveness of the AED in the daily clinical practice.[10,12] Although guidelines for selecting the first AED in newly diagnosed epileptic patients are based on RCTs,[11] RTCs are limited and cannot directly apply to daily clinical practice. In comparison, observational studies are long-term follow-up studies with flexible doses and assess tolerance as well as efficacy of a certain AED,[15,16] however this is less scientific than a double-blind RCT.

This study is an observational study that was followed up for at least 2 years in newly diagnosed patients with cryptogenic partial epilepsy. Both the etiology (symptomatic Vs cryptogenic or idiopathic etiology) and the clinical course of epilepsy (newly diagnosed vs. chronic epilepsy) are a major factors determining the responses to AEDs.[13] These aspects led the authors to look at "cryptogenic partial epilepsy" and "newly diagnosed epilepsy" which is a more homogeneous condition than newly diagnosed partial epilepsy. In addition, cryptogenic partial epilepsy is a common type of partial epilepsy, but the response to AED in cryptogenic partial epilepsy is less well known.

The overall retention rate on the first AED in this study was 51%, which is not significantly different from the previous studies.[9,15,17,18] None of the studies have shown that newer AEDs are more efficacious than the older AEDs, but all of the studies have suggested better tolerance to the newer AEDs than the older AEDs.[10] We expected that the retention on newer AEDs in this study would be better than that on older AEDs. However, our data failed to show a better retention rate on newer AEDs. We think that this was probably due to unbalanced distribution of treatments. As116 patients were on older AEDs (carbamazepine, phenytoin and valproate), whereas only 56 patients were on newer AEDs (lamotrigine, topiramate and oxcarbazepine).

It is very difficult to explain why the presence of epileptiform discharges on the initial EEGs were associated with the failure of retention on the first AED in newly diagnosed cryptogenic partial epilepsy in this study. The presence of epileptiform discharges does not necessarily mean poor response to AEDs in epilepsy. Idiopathic epilepsy, such as, benign childhood epilepsy with centro-temporal spikes or childhood absence epilepsy, shows a very good response to the first AED, even though epileptiform discharges are still noted on the EEG. Furthermore, the fact that the main reason for failure of retention in this study was the lack of tolerance rather than inefficacy of the AEDs led us to conclude that the presence of epileptiform discharges does not directly influence the response to AEDs. However, presence of epileptiform discharges is directly associated with a poor outcome in epilepsy surgery. The presence of pre-operative or post-operative epileptiform discharges in temporal or extra-temporal lobe epilepsy may consistently predict the recurrence of seizures after epilepsy surgery.[19–22] It is a reasonable conclusion that the presence of epileptiform discharges on EEGs, especially in cryptogenic epilepsy that has neither epileptogenic lesion on MRI nor significant insult to the brain before onset of epilepsy, may reflect an active epileptogenic zone. This is partly explains why the presence of epileptiform discharges are associated with the responses to AEDs in this study. The authors analyzed whether the presence of epileptiform discharges on the initial EEG was also associated with the response to AEDs in 217 symptomatic partial epilepsy patients, but failed to find any significant relation between them (data not shown). The epileptogenesis of symptomatic epilepsy may be different from that of cryptogenic epilepsy and the influence of epileptiform discharges on the responses to AEDs may be significant only in cryptogenic partial epilepsy.

This study has limitations. This is a retrospective study and we were not able to obtain information, such as, pre-treatment seizure frequency. Pre-treatment seizure frequency was reported as a very robust clinical factor predicting the response to AEDs in newly diagnosed epilepsy patients.[23] In addition, we failed to show better effectiveness of newer AEDs than older AEDs. The primary goal of this study was not to compare the retention rate between older and newer AEDs but to find the significance of presence of epileptiform discharges on the initial EEG. In the future, a well-designed prospective study should be planned to confirm our results.

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