

# RESEARCH ARTICLE

## Effects of Antiepileptic Drugs on Electroencephalographic Findings in Patients with Idiopathic Generalized Epilepsy

How to Cite this Article: Asadi-Pooya AA, Emami M. Effects of Antiepileptic Drugs on Electroencephalographic Findings in Patients with Idiopathic Generalized Epilepsy. *Iranian Journal of Child Neurology* 2011;5(4):33-36.

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Received: 10 -Agu- 2011  
Last Revised: 14 -Sep- 2011  
Accepted: 21 -Sep- 2011

### Abstract

#### Objective

Several antiepileptic drugs (AEDs) such as phenobarbital (Pb), carbamazepine (CBZ), and valproate (VPA) may suppress interictal epileptiform activity. We investigated the effects of AEDs on electroencephalography (EEG) data from patients with idiopathic generalized epilepsy (IGE).

#### Materials & Methods

In this cross-sectional study, all patients electroclinically diagnosed with IGE were recruited in the outpatient epilepsy clinic at Shiraz University of Medical Sciences from September 2008 through August 2010. A routine EEG was requested at the time of referral for all patients. Statistical analyses were performed using Chi square and Fisher's exact test.

#### Results

This study comprised of 336 patients. For about 20.8% (70 patients) of them, the initial EEG appeared normal. The first EEG was normal in 14.2% of the patients who had newly diagnosed IGE (19 patients). Normal EEG was also detected for 27.6% of the patients who received VPA monotherapy (16 patients), 31% of the patients who received CBZ monotherapy (9 patients), 29.4% of the patients who received Pb monotherapy (5 patients), and 11.1% of the patients who received lamotrigine (LTG) (1 patient).

#### Conclusion

This study shows that compared to LTG, VPA suppresses generalized interictal epileptiform activity in patients with IGE more effectively. Theoretically, if a drug can frequently induce normalization of EEG, then it may be a better drug for treating IGEs.

**Keywords:** Anticonvulsants; electroencephalography; generalized epilepsy

### Introduction

The electroencephalography (EEG) is a test that evaluates the brain's electrical activity. EEG provides information on the presence or absence of abnormal electrical activity as well as information that aids in identification of the disorder and location of the seizure focus. EEG is particularly valuable for diagnosing idiopathic generalized epilepsy (IGE). However, EEG has some limitations. For example, EEG results of some patients with IGE may be normal (1). In addition, several factors may affect the rate and appearance of interictal epileptiform discharges. Several antiepileptic drugs (AEDs) such as phenobarbital (Pb), carbamazepine (CBZ), valproate (VPA),

and levetiracetam may suppress interictal epileptiform activity (2-4). In this study, we investigated the impact of AEDs on EEG data of patients with IGE. Theoretically, this effort may help in the identification of the best possible therapy for patients with IGE.

### Materials & Methods

In this cross-sectional study, all patients who were electro-clinically diagnosed with IGE were recruited in the outpatient epilepsy clinic at Shiraz University of Medical Sciences (the only epilepsy clinic in southern Iran) from 2008 to 2010. The epilepsy diagnosis was based on clinical and EEG findings, and all patients were required to be under the care of our institution's epileptologist. The inclusion criteria had no age constraints, and a routine EEG was requested for all patients at the time of referral. To evaluate the effects of AEDs on EEG activity, we classified the patients into 6 different groups according to the drug status of the patients at the time of referral to our clinic. The 6 groups consisted of patients who were receiving (1) no AED therapy (newly diagnosed), (2) VPA therapy, (3) lamotrigine (LTG) therapy, (4) CBZ therapy, (5) Pb therapy, and (6) any other AED(s) therapy or polytherapy at the time of referral. We excluded the last group from the statistical analysis because of its small numbers and confounding results.

Each patient's age, gender, age at seizure onset, seizure type(s), and EEG results were recorded. The study population was characterized by descriptive summary of demographic variables and relevant clinical and EEG variables. Statistical analyses were performed using Chi square and Fisher's exact tests to determine significance of differences;  $P < 0.05$  was considered significant. This study was approved by the Shiraz University of Medical Sciences Review Board.

### Results

During the 2-year study period, 1640 epilepsy patients were registered at our epilepsy clinic. Of these patients, 344 (21%) were diagnosed with IGE. Of these, 336 (97.7%) patients had an EEG done at our clinic and participated the study. They consisted of 199 (59.2%) female patients and 137 (40.8%) male patients. The age of seizure onset was  $12.3 \pm 6.8$  years (range, 1-47 years).

The group of patients receiving no AED therapy (newly diagnosed) comprised of 134 patients (39.9%). Of the remaining patients, 58 (17%) were receiving VPA, 29 (8.6%) were receiving CBZ, 17 (5%) were receiving Pb, 9 (2.6%) were receiving LTG alone, 15 were receiving LTG with or without other drugs (other than VPA), and 38 (11.3%) were receiving VPA and LTG. Only 7 patients were taking topiramate therapy, and most of them, received topiramate as a part of a polytherapy. None of the patients received levetiracetam or zonisamide since these drugs are not easily available in Iran.

The results of the first EEG performed in this study were normal for 20.8% (70) of the patients. The first EEG was normal in 14.2% (19) of the patients with newly diagnosed IGE, 27.6% (16) of patients in the VPA monotherapy group ( $P = 0.027$ ), 31% (9) of patients in the CBZ monotherapy group ( $P = 0.029$ ), 29.4% (5) of patients in the Pb monotherapy group ( $P = 0.1$ ), and one patient in the LTG group ( $P = 0.8$ ). The frequencies of various EEG abnormalities were not significantly different among the different therapy groups (isolated polyspikes,  $P = 0.25$ ; 3-Hz generalized spike-waves  $\pm$  polyspikes,  $P = 0.16$ ; and 3.5-6 Hz generalized spike-waves  $\pm$  polyspikes,  $P = 0.28$ ). A comparison between EEG abnormalities in patients with newly diagnosed IGE and patients on VPA monotherapy is shown in Table 1. A photoparoxysmal response (PPR) was observed in 11 patients (8.2%) who received no AED (newly diagnosed IGE), 2 patients (3.4%) who received VPA therapy, 5 patients (33.3%) who received LTG, 4 patients who received both VPA and LTG, 1 patient (5.8%) who received Pb, and in none of the patients who received CBZ. The frequency of PPR in patients who received LTG was significantly higher than that in patients who either were newly diagnosed ( $P = 0.01$ ) or received VPA ( $P = 0.01$ ). This was also the case for patients who received LTG monotherapy; of the 9 patients who received LTG monotherapy, 3 exhibited PPR. The differences in the frequencies of PPR in newly diagnosed patients and patients who received the other drugs were not statistically significant.

### Discussion

EEG is a valuable tool for diagnosing IGE. The presence of generalized spike-wave complexes and/or polyspikes increases the probability that IGE will be diagnosed

correctly. However, the use of EEG for diagnosing IGE has several limitations. First, EEG results of some patients may be normal. We observed that the results of first EEGs of about 1/5 (20%) of our patients were normal; this rate was 45% in a previous study (1). This difference may be due to the different methods used during the EEG recordings (e.g., if the filter setting in the EEG machine is set below 70 Hz, then the designated high filter may improperly filter some spikes or polyspikes) or this difference could be reader dependent. Compared to patients who received LTG, patients who received VPA showed a higher frequency of normal EEG; this indicates that VPA suppresses generalized interictal epileptiform activity in IGE patients more effectively than LTG. However, the differences between patients who received VPA and CBZ and between patients who received VPA and Pb were not significant either. In a previous study (2), EEG pairs were identified such that the first tracing illustrated interictal epileptiform activity before AED therapy was initiated. The rate of clearance of interictal epileptiform activity was assessed in the subsequent tracing depending on the drug introduced. EEG pairs ( $n = 213$ ) were identified in patients who received CBZ (55 patients), Pb (81 patients), and VPA (77 patients). Overall, the suppression rates of epileptiform activity in the second EEG were 22% for Pb, 33% for CBZ, and 46% for VPA ( $P = 0.005$  for VPA versus Pb). In a small study, levetiracetam was observed to significantly reduce the epileptiform discharges in the add-on therapy group, but not in the monotherapy group (3). In another small study (8 patients), the authors evaluated the results of continuous EEG of patients with refractory IGE. Four patients received levetiracetam as an add-on therapy, and in four a conversion to levetiracetam monotherapy was undergone. In that study, epileptic activity was analyzed to determine the spike-wave density (spikes/h) and median and maximal duration of spike-wave discharges. Each patient was monitored for 24 hours via EEG before levetiracetam therapy was initiated. Patients were monitored again for 24 hours via EEG after a mean follow-up period of 136 days. Spike-wave density was reduced by 78% following levetiracetam administration, and the median spike-wave duration decreased by 72% ( $P < 0.05$ ) (4). In a case report, a patient with juvenile myoclonic epilepsy demonstrated complete resolution

of myoclonic jerks, absence, and generalized seizures after zonisamide therapy was initiated; his EEG showed near complete resolution of generalized spike-wave discharges after the drug was introduced (5). Additional studies should be conducted to compare the effects of VPA with new AEDs on the EEG findings in patients with IGE. In theory, this may help identify the best possible therapy for these patients, particularly in the refractory cases. In other words, if a drug normalizes EEGs with increased frequency, then it may be the preferred drug for patients with IGE.

In our study, the frequency of PRR for patients in the LTG group was significantly more than that for patients who either were newly diagnosed or received VPA. PRR occurred with increased frequency in the newly diagnosed patients than in patients who received VPA, however, this difference was not significant. VPA has been recommended as the first choice of AED for photosensitive patients (6); this is in concordance with our findings. VPA monotherapy has been shown to be successful in 73%-86% of the treated patients. Levetiracetam is an alternative for patients with IGE and photosensitivity; however, we could not investigate the effects of levetiracetam because none of our patients received this drug. In the literature, clobazam, lamotrigine, ethosuximide, and topiramate have also been recommended as second choices (6). We cannot provide a definite explain for the increased PPR frequency in LTG group compared to newly diagnosed patients; however, the small number of patients may be a potential reason for this difference. LTG should be prescribed carefully until further investigations are conducted that clarify the effectiveness of this drug in photosensitive patients.

**In conclusion,** This study indicates that VPA suppresses generalized interictal epileptiform activity in patients with IGE more effectively than LTG. In theory, a drug that can normalize abnormal EEGs with increased frequency may be a better drug. Thus, we suggest that VPA should be the first choice AED for IGE patients, particularly for patients with photosensitivity. However, LTG should be the first choice of AED for young women because of the potential side effects of VPA (7).

**Limitations of the study**

- a) This was a clinic-based study, and our data may not represent the full spectrum of IGE because patients with mild disease varieties are not always referred to a university clinic. However, the large sample size and the fact that our center is the only epilepsy center in the region may overcome this problem to some extent. Of course, selection bias is always a limitation of this type of study.
- b) Some groups comprised of a small number of patients, which could affect the results.
- c) We did not compare the pre- and post-antiepileptic

drug therapy EEGs in this study. We think that additional studies should be performed to precisely evaluate the effects of various AEDs on EEG data from patients.

**Acknowledgment**

We would like to appreciate Neurosciences Research Center, Shiraz University of Medical Sciences for supporting this study financially.

**Financial Disclosure**

None declared.

**Table 1:** Electroencephalographic (EEG) abnormalities in patients who were newly diagnosed with idiopathic generalized epilepsy (IGE) and patients who received valproate (VPA)

EEG Findings	Newly Diagnosed IGE (n = 134)	VPA Group (n = 58)	P value
3.5-6 Hz Generalized spike wave (GSW)	28	6	0.079
3.5-6 Hz GSW + Polyspikes	25	13	0.549
3 Hz GSW	22	7	0.440
3 Hz GSW + Polyspikes	20	11	0.485
Normal	19	16	0.027
Polyspikes	12	4	0.780
Photoparoxysmal response only	5	0	0.325
Asynchronous F3 & F4 spikes	2	0	1.000
Focal slow waves	1	1	0.514

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