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The Effect of Anti-seizure Drugs on Visual Functions in Epilepsy Patients

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Abstract

Objective: In this study, we aimed to detect early signs of central nervous system involvement in patients with epilepsy, under anti-seizure drug monotherapy, using visual evoked potentials, a non-invasive and easily applicable test, and to correlate these findings with clinical data.

Methods: Between June 10, 2023, and December 31, 2023, 64 patients with epilepsy aged 18 to 65 who had been receiving monotherapy for at least 6 months were included in the study. Additionally, 50 age- and gender-matched healthy individuals were included as a control group. Age, gender, anti-seizure medication, and duration of use, ophthalmologic and neurologic examination findings, and brain magnetic resonance imaging results were recorded. Informed consent was obtained from all participants. Visual evoked potentials of both groups were studied.

Results: The mean age of the patients was 32.39±12.78 years; 51.6% were female, and 48.4% were male. The distribution of medications among the patients was as follows: 59.4% were using levetiracetam, 25% valproic acid, 10.9% lamotrigine, 3.2% carbamazepine, and 1.5% lacosamide. The N75 and P100 latencies and amplitudes in patients were significantly higher than those in the control group ($p<0.05$). P100 latency differences in levetiracetam, carbamazepine and lacosamide users were less pronounced compared to valproic acid and lamotrigine users; however, these differences were not statistically significant ($p>0.05$.).

Conclusion: In this study, levetiracetam, lacosamide, and carbamazepine were found to have less adverse effects on P100 latency, independent of the duration of treatment. For the early diagnosis and treatment of silent visual disturbances, epilepsy patients should undergo visual evoked potential and eye examinations at regular intervals.

Keywords: Levetiracetam, valproic acid, lamotrigine, P100, visual evoked potentials

INTRODUCTION

Visual disturbances are a common side effect of many anti-seizure drugs. Visual impairment in patients with epilepsy may arise from the disease itself or from the effects of the anti-seizure medications (ASMs) used in treatment.

Depending on the drug's properties, some ASMs may cause specific visual problems even at recommended daily doses. ASMs act through gamma-aminobütirik asit (GABA), sodium (Na), chloride (Cl), and calcium pathways. They enhance inhibitory neurotransmission by increasing GABA-mediated Cl transmission, stimulating the glutamic acid decarboxylase enzyme, directly increasing GABA release, or inhibiting GABA reuptake. Valproic acid has a pronounced potentiating effect on GABA-ergic functions.[1] Although the exact mechanism of action of carbamazepine is not fully understood, it has been reported to exhibit anticonvulsant effects by blocking voltage-dependent Na channels.[2,3] Levetiracetam, a second-generation anti-seizure drug, is believed to act by binding to the synaptic vesicle protein synaptic vesicle glycoprotein 2A and interfering with neurotransmitter release from vesicles, while lamotrigine provides neuron stabilization by selectively blocking Na channels and suppressing glutamatergic release.[2,4-7]

GABA is the primary inhibitory neurotransmitter in the brain, affecting up to 70% of the neuronal network and up to 40% of retinal inhibition.[8,9] The GABA inhibitory network in the occipital cortex enhances the selectivity of cortical cells for finer stimuli. This network's role in shaping the visual response to spatial pattern stimuli has been demonstrated by visual evoked potentials (VEPs).[10]

VEPs are particularly useful for detecting clinically silent disorders, identifying lesions, confirming suspicious and ambiguous changes, and monitoring the course of some neurological diseases. They are sensitive, reproducible, non-invasive, and easy to perform.

In the literature, there are studies reporting prolonged P100 latencies after ASM use, as well as studies reporting no change.[11-13] Moreover, most of these studies focused on pediatric patients, leaving unclear the relationship between VEP parameters and ASMs in adults, especially with newer drugs.

The aim of this study was to prospectively detect early and silent signs of central nervous system involvement in patients with epilepsy under anti-seizure drug monotherapy using VEP, a non-invasive and easily applicable test. Additionally, the study aimed to correlate these findings with clinical data.

METHODS

Characteristics of the Patient and Control Groups

The study included 64 epilepsy patients aged 18-65 years, met the inclusion criteria and had been receiving monotherapy for at least 6 months according to the International League Against Epilepsy (ILAE) criteria in our epilepsy outpatient clinic between June 10, 2023 and December 31, 2023. Additionally, 50 age-gender-matched healthy individuals were included as controls.

Patients' age, gender, ASM type and duration, Mini-Mental State test (MMST) results, and brain magnetic resonance imaging (MRI) examinations were recorded.

Participants included in this study were individuals aged 18 and over, who had been diagnosed with epilepsy for at least six months according to the ILAE diagnostic criteria, were on monotherapy, and had normal neurological and visual examinations, as well as normal MMST and MRI results. Additionally, participants had not experienced a seizure in the three days prior to the measurement. Exclusion criteria included individuals with neurological, systemic, toxic, traumatic, autoimmune, endocrinological, syndromic, or metabolic diseases; those taking chronic medications affecting the central nervous system (e.g., antiepileptics, neuroleptics, psychostimulants, analgesics, steroids, sedative-hypnotics); individuals with significant eye damage (visual acuity between 0.9 and 1.0, including correction with glasses); individuals who were underweight [body mass index (BMI) <18.5 kg/m^2] or overweight (BMI ≥35 kg/m^2); those with head trauma, intracranial malformations, or space-occupying lesions; those with abnormal MRI findings; and individuals with a history of psychiatric illness. The control group consisted of healthy individuals aged 18 and over who had no neurological, psychiatric, or metabolic diseases, no history of drug, alcohol, or substance addiction, and normal MRI results.

Informed consent was obtained from all participants. The study was approved by the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 2629, date: 08.06.2023).

VEP procedure was conducted according to the International Federation of Clinical Neurophysiology guidelines.[14]

The VEP study was performed using the Cadwell Sierra Summit System (Cadwell Laboratories, Kennewick, Washington, USA).[15]

MAIN POINTS

- Anti-seizure medications (ASMs) affected visual evoked potential parameters, particularly causing a delay in P100 latency.
- Levetiracetam, lacosamide, and carbamazepine had a less negative effect on P100 latency, regardless of treatment duration.
- Information regarding the silent visual effects of ASMs in adult patients is still insufficient and more studies are needed in this area.

Silver cup electrodes were used for recording, with high-pass and low-pass filters set to 1 Hz and 100 Hz, respectively. Sensitivity and scan rate were set to 5 μV/division and 25 ms/division, respectively. The Oz and Fz points were marked according to the international 10-20 electroencephalography system, and electrodes were placed at the active Oz and reference Fz. VEP test impedances were <5 kΩ for all electrodes. For pattern-reversal VEP, a CBOX 18.5 LED monitor displaying a black and white checkerboard, with a red dot in the center was used, and the stimulus rate was set to 1 Hz.

N75, P100, and N145 waves were analyzed by setting the distance between the LED monitor and the participants' eyes to 100 cm and the control size to 51 minutes of arc (dimensions 8x8). VEP was applied to both eyes in a dark room. VEP waves were obtained by averaging at least 100 potentials twice, for each eye. P100 amplitudes were calculated by measuring from N75 to P100.

Statistical Analysis

Descriptive statistics included frequency, percentage, arithmetic mean, and standard deviation. The chi-square test was used for categorical variable comparisons. The independent sample t-test was used to compare values between the case and control groups. Kruskal-Wallis analysis, which is a non-parametric test, was performed due to the non-homogeneous distribution of the case group based on drug use. Spearman correlation analysis was used to evaluate the relationship between values in the case group. IBM Statistical Package for the Social Sciences 21.0 (IBM Co. Armonk, NewYork) package was used for statistical analysis of the data. A p-value below 0.05 was considered statistically significant.

RESULTS

Among the patients, 51.6% (33) were female and 48.4% (31) were male, with a mean age of 32.39±12.78 years. In the control group, 70% (35) were female and 30% (15) were male, with a mean age of 36.32±11.85 years. Forty five patients (70.3%) had generalized seizures, 15 patients (23.4%) had focal seizures without awareness, and 4 patients (6.25%) had focal seizures with preserved awareness (Table 1).

No statistically significant difference was found between the gender groups (χ^2=3.561; p=0.074) and average age (t=0.901; p=0.370) of the case and control groups.

Regarding medication usage among the patients, 59.4% (38) were using levetiracetam, 25% (16) were using valproic acid, 10.9% (7) were using lamotrigine, 3.2% (2) were using carbamazepine, and 1.5% (1) were using lacosamide.

N75 and P100 latencies, and amplitudes were found to be statistically significantly higher in the patient group compared to the control group (Table 2).

By excluding patients using lacosamide and carbamazepine in the analysis of the case group (because the number of patients in this group was small and disrupted the homogeneous distribution), no significant difference was detected between the type of drug used and VEP parameters (p>0.05) (Table 3).

Levetiracetam users (mean P100 latency: 3.60±3.07) had a shorter P100 latency compared to valproic acid (4.70±3.24) and

lamotrigine (4.03±3.20) users. However, these differences were not statistically significant (p>0.05) (Figure 1).

No significant correlation was found between VEP parameters and treatment duration in the patient group (Spearman correlation analysis). There was no statistically significant difference in VEP latencies between different seizure types (p>0.05). Additionally, no significant difference was found among other parameters within the patient group concerning the type of drug used (p>0.05).

DISCUSSION

It is estimated that approximately 50 million people worldwide have epilepsy, and 4.9 million people will receive a new diagnosis of epilepsy each year.[16,17] When prescribing ASMs, the goal is to achieve maximum seizure control with minimal side effects.

VEPs are a sensitive non-invasive method for evaluating the effects of ASMs on the central nervous system. The literature contains a limited number of studies on the impact of ASMs on VEPs, and the findings are often conflicting. This study is the first to examine the effects of multiple ASMs on visual function in a group of adult patients treated with more than three different ASMs concurrently.

Harding et al.[18] found results similar to the placebo after administering valproic acid to 10 volunteers for a maximum of 14 days, and stated that valproic acid had no effect on VEPs latencies. However, in subsequent studies, it was determined that there was no difference in VEPs latency and amplitude between the healthy group and the epileptic groups before the initiation of ASM. VEPs P100 latency was prolonged after treatment; this could be attributed to ASMs.[11,12] Therefore, we selected our study

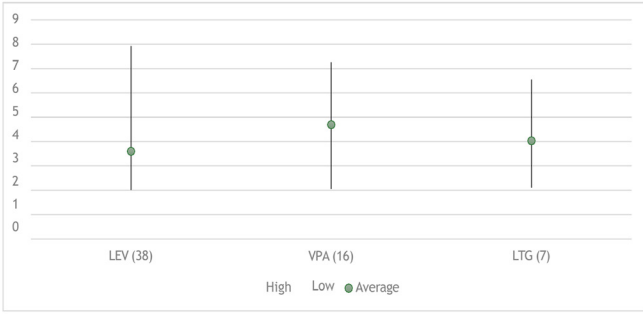

Figure 1. Right-left P100 latency differences

Table 1. Homogeneity and descriptive characteristics of case and control groups

Groups	Gender		Age	
	Female n (%*)	Male n (%*)	x̄	SD
Control (50)	35 (70.0%)	15 (30.0%)	36.32	11.85
Case (64)	33 (61.6%)	31 (48.4%)	32.39	12.78
Test values	χ^2**=3.561, p=0.074		t***=0.901, p=0.370	

*Percentage of rows **Chi-square test. ***Independent sample t-test, SD: Standard deviation

Table 2. Comparison of case and control groups

	Control (50)		Case (64)		Test values	
Variables	**x̄**	**SD**	**x̄**	**SD**	**t***	**p-value**
N75 right latency	54.30	7.19	57.97	13.10	-3.812	**0.000**
N75 left latency	55.40	7.38	63.61	43.34	-4.615	**0.000**
Right-left N75 latency difference	4.15	3.46	7.72	11.56	-6.547	**0.000**
P100 right & left latancy averages	86.65	6.32	101.33	13.64	-4.649	**0.000**
Right-left P100 latency difference	3.61	2.58	5.25	3.66	-5.836	**0.000**
N145 right	128.99	18.22	130.26	16.75	-1.294	**0.075**
N145 left	130.38	16.31	132.22	22.13	-1.008	**0.082**
Right-left N145 latency difference	5.86	3.94	6.95	7.29	-4.551	**0.000**
N75/P100 amplitude difference	1.31	1.26	2.18	1.97	-6.640	**0.000**

*Independent sample t-test, SD: Standard deviation

Table 3. Evaluation of the drug type used in the case group according to parameters

Variables	Levetiracetam (38)		Valproic acid (16)		Lamotrigine (7)		p-value*
	x̄	SD	x̄	SD	x̄	SD	
Right-left N75 latency difference	7.28	9.42	7.26	8.91	8.18	6.24	0.710
Right-left P100 latency difference	3.60	3.07	4.70	3.24	4.03	3.20	0.862
Rigt-left N145 latency difference	7.60	2.21	6.75	6.21	7.14	4.18	0.258
N75-P100 amplitude difference	2.60	1.83	2.06	1.27	2.28	1.49	0.057

*One-way analysis of variance note: in the lacosamide and carbamazepine (3) group, right-left N75 latency difference was (7.01±7.33), right-left P100 latency difference (3.45±2.51), right-left N145 latency difference (6.29±3.31), N75-P100 amplitude difference (3.00±1.11) was determined.
SD: Standard deviations

population from patients under effective ASM treatment. The study group consisted of these patients, while healthy volunteers with a homogeneous distribution constituted the control group.

Verrotti et al.[11] compared two groups: 58 children with epilepsy who were treated with carbamazepine, valproic acid, and phenobarbital for one year, and 50 controls. They found P100 latency prolongation in those treated with carbamazepine and valproic acid. Another study involving 53 patients using carbamazepine, valproic acid, and levetiracetam, along with 20 controls, found significant P100 latency prolongation in the ASM group compared to controls. It was noted that levetiracetam had a lesser impact on P100 latencies in epileptic patients, compared to valproic acid and carbamazepine.[19] Two recent studies with patients using only levetiracetam reported no significant difference in P100 latencies compared to the control group; however, these studies involved very small sample sizes.[20,21]

In this study, we observed a statistically significant prolongation of VEPs latencies (N75, P100) in epileptic patients using ASM compared to the control group ($p<0.05$).[11,19] However, there was no difference between the types of drugs used in terms of prolongation of VEP latencies ($p>0.05$) (Table 3).

Although lamotrigine is a broad-spectrum, new-generation ASM frequently preferred for women of childbearing age and during pregnancy, we did not find any previous studies on lamotrigine's effects. Although our study did not reach statistical significance, it found that P100 latency prolongation in lamotrigine users is similar to that in valproic acid users.

Additionally, we observed a significant increase in amplitudes in the patient group compared to the control group ($p<0.05$). A study reported higher VEP amplitudes in the right and left eyes of 18 pediatric patients using levetiracetam compared to 24 healthy children.[20] However, it is evident that more work is needed on this subject.

Finally, our study found no significant effect of treatment duration on VEP latencies.[20]

As can be seen, no consistently accepted conclusion has yet been reached in the literature on this subject. These inconsistencies may be partly due to differences in research techniques (flash or pattern VEPs) and patient population, as well as the possible effects of anticonvulsant drugs and the nature of the underlying cause.

Study Limitations

Although we selected both our study group and control group, by excluding those with conditions that could affect VEPs findings, the most important limitation of our study is the absence of VEPs findings in our patients before treatment. However, there were also similar sample selections reported in the literature.[19-21] Although our sample is larger than many studies, larger scale and longer follow-up studies are needed to make a detailed assessment.

CONCLUSION

We found that ASMs affected VEPs parameters, particularly P100 latency. Levetiracetam had a less negative effect on P100 latency, although the difference did not reach statistical significance. Most studies in the literature have focused on pediatric patients, with a limited number of studies including adults. Our study provides important information about the effects of ASMs on VEPs parameters in adult patients. We recommend that these findings be considered when choosing treatment options and that regular (at least annual) VEPs and eye examinations be conducted in epilepsy patients using ASMs. This may help in early diagnosis and treatment of silent visual disturbances.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 2629, date: 08.06.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.B.B., D.T., Concept: P.B.B., Design: P.B.B., D.T., Data Collection or Processing: P.B.B., D.T., Analysis or Interpretation: P.B.B., Literature Search: P.B.B., D.T., Writing: P.B.B., D.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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