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Examining the Effect of Anti-seizure Medications Monotherapy on Cognitive Functions in Patients with Epilepsy: A 1-month Longitudinal Study

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Abstract

Objective: Cognitive impairment in epilepsy is one of the most important problems affecting daily life. This study aimed to investigate the change in cognitive functions of patients with epilepsy a month after starting anti-seizure medications (ASMs).

Methods: Patients with epilepsy who started treatment with ASMs were included. The general cognitive status, attention, memory, executive functions, and language skills of epilepsy patients were evaluated with detailed neuropsychological tests before and one month after the initiation of ASMs.

Results: The study included 14 patients with epilepsy. The patients showed increased attention, visual memory, and inhibition skills 1 month after using ASMs compared to pre-treatment status.

Conclusion: Appropriate and successful treatment of epilepsy patients can improve cognitive performance in the short term. However, long-term longitudinal studies are needed to support these findings.

Keywords: Antiseizure medications, cognitive impairment, epilepsy, monotherapy

INTRODUCTION

Cognitive impairment is one of the major problems experienced by people with epilepsy.[1] Cognitive impairment is associated with many causes. Factors such as seizure characteristics, age of onset of epilepsy, location of epileptic activity, type of epilepsy, number or type of anti-seizure medications (ASMs), and individual characteristics contribute to the occurrence of cognitive impairment.[2] Patients with epilepsy have impairments in memory, visual-spatial functions, executive functions, attention, information processing speed, and naming skills.[3-5]

Experts emphasise that ASMs may be the cause of cognitive impairment. Additionally, cognitive impairments may be observed when epilepsy is not controlled with ASMs.[2,6]

Many studies have shown a decline in cognitive functions in long-term chronic epilepsy.[7] However, it is also stated that in new-onset epilepsy, existing cognitive capacity/status can be preserved with early and successful treatment.[8-10]

Considering all these, there is a need for longitudinal studies in which many factors are considered for an in-depth examination of cognitive functions in epilepsy. In this study, we aimed to examine the changes in cognitive functions by applying comprehensive neuropsychological tests to newly diagnosed epilepsy patients before, and 30 days after treatment.

METHODS

Participants

This study was carried out at a university hospital, in the department of neurology, epilepsy centre, between 2019 and 2020. Neurological examination and neuropsychological evaluation were performed on patients diagnosed with epilepsy before using ASMs. Neuropsychological evaluations were repeated in patients 30 days after they started using ASMs. The seizure type, classification of epilepsy, type of ASMs, and seizure frequency were noted. Patients with any psychiatric or neurological diseases, and patients undergoing epilepsy surgery were excluded.

Neurological and clinical examinations of the patients were performed by a clinical neurophysiologist, and neuropsychological evaluations were performed by a neuropsychologist.

This study's compliance with ethical standards was approved by the Dokuz Eylül University Ethics Committee (decision no: 2021/22-29, date: 28.07.2021).

Neuropsychological Assessment

In our previous cross-sectional study, the neuropsychological assessment tools used were described in detail.[5] In summary, the cognitive functions of all participants were evaluated. General cognitive status was evaluated with the Mini-Mental State Examination,[11,12] and attention was assessed with digit span, (forward and backward digit span), and the Wechsler Memory Scale (WMS) mental control subtests.[13,14] Episodic verbal memory was measured by the Oktem Verbal Memory Processes test, and visual memory was measured by the WMS visual reproduction subtest.[13,14] For executive functions, verbal fluency tests (phonemic and semantic), Stroop test TBAG form, clock drawing, similarity, and proverb interpretation tests.[16-20] Naming ability was evaluated with the Boston Naming test.[21] For depression and anxiety symptoms, the Beck Depression Scale and the Beck Anxiety Scale were used.[22-25]

Statistical Analysis

The data of this study were analyzed in the Statistical Package for the Social Science version 24 (Armonk, NY: IBM Corp.). Normal distribution of the data was examined with the Kolmogorov-Smirnov test. Data that did not meet normal distribution conditions were examined with the repeated measures Wilcoxon signed-rank test. $P<0.05$ is used for statistical significance.

RESULTS

Fourteen patients were included. Ten of the patients (71.4%) were female, the median age was 28 (minimum-maximum, 20-54). Eight of the patients (57.2%) have focal epilepsy which is the most frequent epilepsy syndrome. Six of the patients (42.8%) use new-generation ASMs which of 4 (28.6%) use levetiracetam (LEV) and 2 (14.3%) use lamotrigine (LTG) whereas, 8 of them (57.2%) use classical ASMs which of 6 (42.9%) use carbamazepine (CBZ) and of 2 (14.3%) use valproic aside (VPA). The demographic data, seizure classifications, seizure types, and dosage of ASMs ratios of the participants are presented in Table 1.

Statistically significant differences were found in WMS-R mental control 5 ($Z=-2.945$, $p=0.003$), WMS-R immediate ($Z=-2.434$, $p=0.015$), WMS-R delayed ($Z=-2.373$, $p=0.018$), Stroop test interference ($Z=-2.355$, $p=0.019$), between pre- and post-treatment in epilepsy patients. The mean, standard deviation, and statistical values of neuropsychological test scores are presented in Table 2.

The mean scores of the neuropsychological tests of epilepsy patients receiving both classical and new-generation ASMs were compared before and after treatment. No statistically significant difference was found in terms of cognitive functions in epilepsy patients receiving classical-generation ASMs before and after

Table 1. Clinical and demographical features

Epilepsy patients (n=14)	Value
Age (mean±SD)	33.14±12.65
Education (years) (mean±SD)	11.36±3.20
Gender n (%)	
Male	4 (28.6%)
Female	10 (71.4%)
Handedness n (%)	
Right	12 (85.7%)
Left	2 (14.3%)
Epilepsy classification n (%)	
Focal	8 (57.2%)
JME	2 (14.3%)
JAE	1 (7.1%)
GTCA	2 (14.3%)
Unknown	1 (7.1%)
Seizure type n (%)	
Generalized	5 (35.7%)
Focal	8 (57.1%)
Unknown	1 (7.1%)
Seizure frequency n (%)	
Seizure free	7 (50.0%)
Occasionally	6 (42.9%)
Frequently	1 (7.1%)
EEG findings n (%)	
Epileptic abnormality	6 (42.9%)
No epileptiform activity	7 (50.0%)
Antiseizure medications	**Distribution n (%)**
LEV	4 (28.6%)
CBZ	6 (42.9%)
VPA	2 (14.3%)
LTG	2 (14.3%)

The table presents the means or proportions of demographic and clinical data. Seizure-free means <1 per year, occasionally <1 per week to >1 per year, and frequently means >1 per week in seizure frequency.
EEG: Electroencephalography, GTCA: Generalized tonic-clonic seizures alone, JME: Juvenile myoclonic epilepsy, JAE: Juvenile absence epilepsy, LEV: Levetiracetam, CBZ: Carbamazepine, VPA: Valproic acid, LTG: Lamotrigine

MAIN POINTS

- The strongest aspect of this study is that it examined the cognitive functions of epilepsy patients longitudinally.
- Significant improvements in attention, executive functions, visual memory and mood were found after antiseizure post-treatment compared to pre-treatment.
- This study shed light on subsequent longitudinal studies.

Table 2. Scores of neuropsychological tests and mood

Neuropsychological tests	Pre-treatment	Post-treatment	Z	p
Global cognition				
MMSE	29.15±1.14	29.21±1.18	0.00	1.00
Attention				
Forward digit span	5.71±1.20	5.57±1.08	-0.513	0.608
Backward digit span	4.00±1.30	4.07±0.99	-0.439	0.660
WMS-R mental control 1	6.86±2.71	6.64±2.73	-0.522	0.601
WMS-R mental control 2	4.21±1.80	3.78±1.96	-0.915	0.360
WMS-R mental control 3	22.07±20.46	14.16±7.34	-0.892	0.373
WMS-R mental control 4	24.86±16.12	22.5±12.53	-1.417	0.156
WMS-R mental control 5	81.17±43.45	61.25±29.08	-2.945	**0.003**
Verbal memory				
OVMPT first recall	5.79±1.92	6.07±1.85	-0.672	0.502
OVMPT highest recall	14.36±1.64	14.14±2.14	-1.134	0.257
OVMPT reaching criteria	4.86±2.95	4.57±3.47	-0.511	0.610
OVMPT total learning	118.07±16.72	119.0±21.73	-0.315	0.753
OVMPT recall	12.93±1.77	12.07±3.31	-1.030	0.303
OVMPT recognition	2.07±1.77	2.85±3.08	-1.030	0.303
Visual memory				
WMS-R immediate	11.073.81	12.16±3.83	-2.434	**0.015**
WMS-R delayed	11.07±4.02	12.08±4.10	-2.373	**0.018**
Executive functions				
Verbal categorical fluency	19.43±6.72	20.92±6.92	-1.260	0.208
Letter fluency	33.36±19.87	36.14±18.10	-1.385	0.166
Stroop test interference	57.71±30.19	46.35±20.28	-2.355	**0.019**
Similarity	9.08±2.23	9.46±2.22	-1.155	0.248
Abstraction	2.86±0.36	2.64±0.92	-1.342	0.180
Clock drawing	9.43±0.93	9.42±0.93	-0.0	1.00
Language				
Naming	14.09±1.81	14.23±1.53	-0.577	0.564
Mood				
Beck Depression Scale	14.64±11.31	13.14±8.87	-0.525	0.599
Beck Anxiety Scale	17.29±12.93	11.85±9.86	-2.267	**0.023**

The mean and standard deviation of all neuropsychological tests are presented. The p value was set to <0.05. The Z-value indicates the Wilcoxon-signed rank test. Bold values indicate p<0.05.
MMSE: The Mini-Mental State Examination, WMS-R: The Wechsler Memory Scale-Revised, OVMPT: Oktem Verbal Memory Processes test, Stroop test (condition: the time required for color naming)

treatment (p>0.05). Statistically significant differences were found in the cognitive functions of epilepsy patients receiving new-generation ASMs before and after treatment (p>0.05). A significant change was found in the WMS-R mental control 5 [t(5)=2.849, p=0.036], Stroop test interference duration [t(5)=7.228, p=0.001] and Similarity tests [t(5)=-5.00, p=0.038] of the epilepsy patients receiving newer-generation ASMs compared to before treatment. Figure 1 shows a flow chart.

DISCUSSION

Our results showed that in epilepsy patients who started new-onset ASMs, sustained attention, visual memory, and inhibition skills increased after 1 month of monotherapy. Many studies have indicated that high doses of polytherapy lead to impaired cognitive functions compared to monotherapy in epilepsy.[4,26-30] The results of our study are consistent with these findings. Mean cognitive function scores measured at baseline were within the normal range according to age and educational neuropsychological test norms in newly treated epilepsy patients. However, a significant increase was found in the previously mentioned cognitive test scores in measurements made 1 month after ASMs treatment. These results are important, showing that appropriate and successful treatment, in epilepsy patients does not worsen cognitive functions over a short period. However, longer-term longitudinal studies are necessary to reveal changes in cognitive functions in patients with epilepsy.

ASMs and cognition-based studies have shown that LTG and LEV have less adverse effects on cognitive functions, while CBZ, valproate, and phenytoin, which are the classical ASMs,

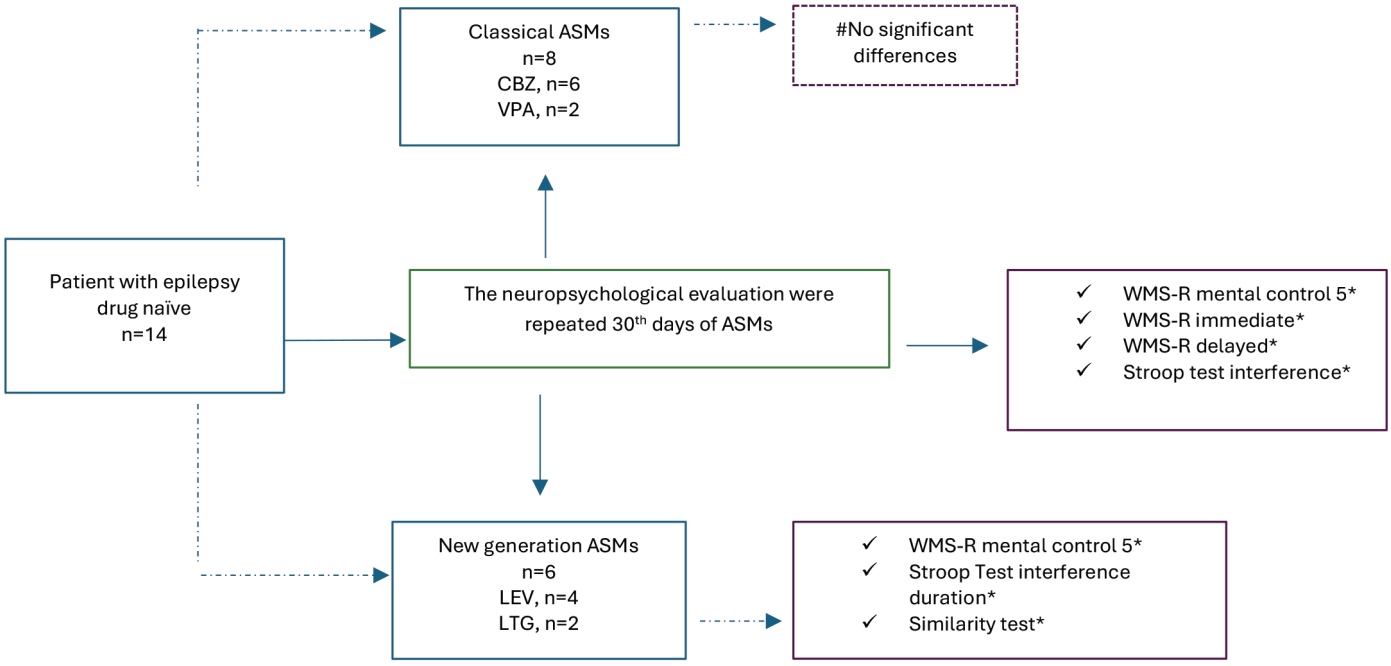

Figure 1. Flow chart of the study and is shown significant differences neuropsychological assessment
*p<0.05.
ASMs: Anti-seizure medications, CBZ: Carbamazepine, LEV: Levetiracetam, LTG: Lamotrigine, VPA: Valproic aside, WMS-R: The Wechsler Memory Scale-Revised

have more adverse effects on cognitive functions.[5,30-36] Consistent with the literature, our study observedthat LTG and LEV, which are considered new-generation ASMs, increased attention and executive functions in a one-month longitudinal examination. However, CBZ and VPA, which are considered classical-ASMs, did not show a significant difference in cognitive functions. This finding is not consistent with the literature. The small number of our epilepsy patients and the short-term use of ASMs may have caused these results. Especially, topiramate was reported to have the highest negative effect on cognitive functions.[36] The effects of ASMs on cognitive functions could not be examined separately due to the small number of participants in this study.

Difficulties in cognitive domains such as verbal memory, visual memory, executive functions, attention, working memory, and language have been generally reported in individuals with epilepsy.[2,26-28] Although the control groups in the studies revealing these findings consisted of healthy individuals or individuals with mild cognitive impairment or epilepsy subtypes, the reported involvement of cognitive difficulties was almost similar. Memory impairments occur more in temporal epilepsy, and executive function impairment occurs in frontal epilepsy.[37,38] A good definition of disease-related factors such as the type of epilepsy, medications used, duration of epilepsy, and methodological factors such as neuropsychological measurement tools and number of participants that may affect cognition, is crucial for understanding the extent to which cognitive functions are affected in epilepsy.

It was stated that the general cognitive capacity of epilepsy patients is lower than controls before the diagnosis of epilepsy.[39-43] A longitudinal study showed that memory functions were lower in drug-resistant focal epilepsy patients compared to healthy controls even after 4.8 years.[43] It is estimated that patients with drug-resistant epilepsy discontinuing current treatment, the possibility of evaluating new treatment options, and uncontrolled seizures contribute to cognitive dysfunction.[44] Therefore, it is suggested that cognitive disorders seen in patients with treatment-resistant epilepsy are different from cognitive disorders in individuals with epilepsy.[2] In another longitudinal study that included 2-10 years of follow-up of temporal epilepsy patients receiving medical and surgical treatment, it was shown that memory functions decreased over time in both groups, while there was no significant change in other cognitive domains.[45]

Although longitudinal studies with long-term follow-up have shown a decline in cognition over time, many factors affect these results. Increasing age, chronic epilepsy, increased doses of medication, polytherapy for epilepsy treatment, uncontrolled seizures, and other features that may change in the long term may contribute to deterioration in cognitive functions. Our study provides preliminary findings on the short-term results of anti-seizure monotherapy in a heterogeneous epilepsy group. For future studies with larger numbers of participants, longer follow-ups are needed.

Study Limitations

An important limitation of this study is the small number of participants. The small number of participants made it difficult to examine in depth the disease-related factors on cognitive functions.

CONCLUSION

Many factors contribute to cognitive impairment in epilepsy. Longitudinal studies of patients with epilepsy help differentiate

factors such as intra-individual and inter-individual variability, as well as treatment effectiveness. A one-month longitudinal study of patients with epilepsy has shown an improvement in cognitive abilities. However, this is a preliminary study. Longer-term studies with more participants may shed light on the relationship between epilepsy and cognitive impairment.

Ethics

Ethics Committee Approval: This study's compliance with ethical standards was approved by the Dokuz Eylül University Ethics Committee (decision no: 2021/22-29, date: 28.07.2021).

Informed Consent: A written informed consent form was obtained from each patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.M.D., İ.Ö., B.B., Concept: H.E.B., D.M.D., İ.Ö., B.B., Design: H.E.B., D.M.D., İ.Ö., B.B., Data Collection or Processing: H.E.B., D.M.D., İ.Ö., B.B., Analysis or Interpretation: H.E.B., D.M.D., İ.Ö., B.B., Literature Search: H.E.B., D.M.D., İ.Ö., B.B., Writing: H.E.B., D.M.D., İ.Ö., B.B.

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