Evaluation of the Effect of Anti-seizure Drugs on Cognition in Patients with Idiopathic Generalized Epilepsy by Digital Neuropsychological Test

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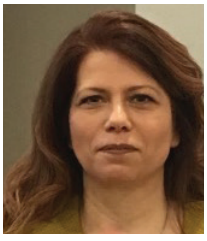

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Abstract

Objective: Cognitive impairment in patients with epilepsy appears as epileptic seizures or side effects of anti-seizure drugs (ASD). The aim of this study was to evaluate the cognitive functions of idiopathic generalized/genetic epilepsy (IGE) patients with digital neuropsychological tests (DNT) and to reveal whether there are differences in test batteries in patients using ASD with monotherapy or polytherapy.

Methods: Thirty-nine individuals diagnosed with IGE syndrome in our clinic, who were diagnosed with IGE in the last decade and had completed at least eight years of education, were included in the study. After the Standardized Mini-Mental Test and Beck Depression Inventory, for neurocognitive evaluation, TestMyBrain (TMB) Number Range, TMB Selective Response Speed Test, TMB Visual Association Pairs Test, TMB Matrix Reasoning and TMB Number Symbol Matching Tests of TMB DNT Battery were applied to all participants.

Results: Among the test categories in the current test battery that measure cognitive functionality in the areas of attention, short-term memory, working memory, visual memory, episodic memory, cognitive processing speed, selective response/inhibition, fluent cognitive skills and perceptual reasoning were applied to the patients and no significant difference was found between the groups receiving monotherapy or polytherapy ($p<0.05$).

Conclusion: It was concluded that the performance status of IGE patients in the sub-category tests included in the TMB DNT Battery and evaluated according to visual material was independent of the number of drugs, but this situation could not be independent of education.

Keywords: Digital neuropsychology, idiopathic generalized epilepsy, cognitive functions

INTRODUCTION

Idiopathic/genetic generalized epilepsies (IGE) account for approximately one-third of all epilepsies and may be of varying phenotypes, depending on age, and are cathegorized as Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) or IGE with Tonic-Clonic Seizures only.[1] Most of these begin in childhood or adolescence. IGE is characterized by the absence of intellectual disability and focal neurological deficits. However, some studies, mostly consisting of JME patients, have reported impairments in working memory, verbal fluency, response inhibition, sustained attention, and visuospatial reasoning in IGE patients.[2-4]

Cognitive changes seen in epilepsy patients are not only related to seizures, but may also occur as a side effect of anti-seizure drugs (ASDs). Variables including polytherapy being the drug regimen, high level dosage and ASDs' blood levels are also important here. Most major ASDs administered at therapeutic doses do not usually cause cognitive or behavioral impairment. However, individual variability is significant, and some patients cannot tolerate low serum drug levels, while others can tolerate high levels of the same drug without subjective or objective side effects.[5] The aim of this study was to evaluate the potential effect of ASDs on cognition by applying tests that prioritize visual memory and to reveal whether there is a difference between these tests in patients who have been treated with monotherapy or polytherapy.

METHODS

The study group consisted of patients with IGE who were treated in the epilepsy outpatient clinic of the Neurology Department of Marmara University Faculty of Medicine. The study began during the first phase of the Coronavirus disease-2019 (COVID-19) pandemic.

Patients between the ages of 18-48 who had at least 8 years of education were selected from 80 patients who were diagnosed with IGE in our clinic and had been followed up regularly in the last year. Due to the COVID-19 pandemic, 50 patients who met the study criteria were contacted by phone and informed about the test, but 11 of 50 patients refused to participate in the study due to pandemic conditions, and the remaining 39 patients did participated in the study. Of these patients, 35 were JME and 4 were JAA patients. Because of the free use of the TestMyBrain (TMB) Digital Neuropsychology Test (DNT) Battery by McLean Hospital and Harvard University Medical School Brain and Cognitive Health Technologies Laboratory in cooperation with the Many Brains Project during the COVID-19 pandemic, this battery was released to patients after obtaining the necessary permissions. Before participating in the study, all volunteer patients were informed about the study and a voluntary consent form was obtained. Observing the pandemic precautions, the patients were first administered the Beck Depression Inventory (BDI) and the Standardized Mini-Mental Test, and then digital tests that prioritize visual memory. As part of the DNT, participants were asked to complete five tests: TMB Number Range, TMB Selective Response Speed Test, TMB Visual Association Pairs Test, TMB Matrix Reasoning, and TMB Number Symbol Matching Test. The battery included tests for short-term visual, episodic and working memory, attention, processing speed, crystallized and fluid intelligence, response selection/inhibition, and attention.[6] The tests were completed over an average of 40 min.

TMB Digit Span: TMB Digit Span involves recall sequences of digits of increasing length, either in the same order as presented (digit span forward-DSF) or in the opposite order (digit span backward-DSB). TMB Digit Span measures short-term memory, attention, and working memory (backward version).

TMB Choice Reaction Time Test: TMB Choice Reaction Time Test (CRT) is a standard format CRT task. CRT measures processing speed, response selection/inhibition and attention. This test measures both the reaction time (CRT.RT) and accuracy (CRT. ACC).

TMB Visual Paired Associates Test: TMB Visual Paired Associates Test (VIS) is adapted from standard paradigms for assessing context-specific encoding and memory retrieval, which assesses visual memory and episodic memory. The primary result measure of VIS is accuracy, in terms of proportion correct or number correct out of 24 trials.

TMB Matrix Reasoning: TMB Matrix Reasoning (MAT) identifies the image that best completes the pattern in a series, based on a logical rule. This test measures fluid cognitive ability and perceptual reasoning. The main result measure of this test is accuracy, in terms of proportion correct or number correct.

TMB Digit Symbol Matching: TMB Digit Symbol Matching (DSM) involves a symbol-number key. The participants are expected to match as many symbols and numbers as possible within 90 seconds. DSM measures the processing speed. The main result measure of DSM is the number of trials correctly completed within 90 seconds, which is proportionate to the mean response time.

Ethics Committee: The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Marmara University Faculty of Medicine Clinical Research Ethics Committee approved the study (number: 09.2021.329, date: 09.04.2021).

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences 25 software package. Frequency and percentage values are given for demographic variables. The normality assumption was evaluated with the Shapiro-Wilk test. Independent sample t-test was used for data showing normal distribution and Mann-Whitney U test was used for data not showing normal distribution to evaluate age groups and monotherapy and polytherapy groups. Statistical significance was accepted as p value <0.05.

RESULTS

Of the 39 IGE patients included in the study, 21 (53.9%) were female and 18 (46.1%) were male (Table 1) with a mean age of 23.38±7.10 (minimum=20, maximum=49), 23 of the patients were under 25 years old and 16 of them were 25 years and older. According to their education level, 20.5% of the patients had 8 years, 23.1% had 12 years and 56.4% had more than 12 years of education (Table 1). Epileptiform disorder was seen in 20 of 39 patients' electroencephalographies taken within the last year. Of these patients, 13 were receiving polytherapy and 7 were receiving monotherapy.

The mean values of DSF, DSB, CRT.RT, CRT.ACC, VIS, MAT and DSM in monotherapy and polytherapy groups are shown in Table 2, and no significant difference was found between the two groups in terms of these tests (p>0.05). There was no significant difference between monotherapy and polytherapy groups in terms of BDI results (p=0.872).

Table 1. Demographic characteristics of the participants

The number of participants (n=36)	f	%
Gender		
Female	21	53.9
Male	18	46.1
Age		
<25	23	59
>25	16	41
Education level		
8 years	8	20.5
9-12 years	9	23.1
>12 years	22	56.4

MAIN POINTS

- Cognitive dysfunction is one of the most common complaints in patients with epilepsy.
- When we evaluated executive function, attention and concentration functions in idiopathic/genetic generalized epilepsies patients using the digital neuropsychological test battery, it was found that there was no difference between monotherapy and polytherapy groups.
- However, it has been observed that a high level of education has a positive effect on the success obtained from the tests.

The data of DSF, DSB, CRT.RT, CRT.ACC, VIS, MAT and DSM values according to age groups (<25 years; 25≥) are given in Table 3, and no significant difference was found between the two groups in terms of these tests (p>0.05).

There was no significant difference in DSF, DSB, CRT.RT, CRT. ACC, VIS, MAT and DSM values between sodium valproate, lamotrigine and levetiracetam used in monotherapy (p>0.05).

However, when the patients were categorized as ≤12 years and 12> years according to their education level, there were statistically differences in DSB, CRT.RT, MAT and DSM values, DSF, MAT and DSM values were higher and CRT.RT values were lower in the higher education group, and statistical significance was found at the highest level especially in the MAT evaluation. In line with these results, short-term memory, attention and working memory evaluated by DSF (p=0.02), processing speed performance evaluated by DSM (p=0.03) and perceptual reasoning measured by the MAT test was found to be significantly higher in the high-education group (p=0.0001). In the CRT-RT test, in which attention was evaluated, it was noted that the reaction time was shorter (p=0.047) (Table 4).

It was found that the reaction time was significantly longer in the CRT-RT test, in which attention was evaluated, in patients aged 25 and over who received polytherapy compared to patients who received monotherapy (p=0.021). Relevant data are given in Table 5.

Table 2. Comparison of digital neuropsychological test subcategories between monotherapy and polytherapy groups

Digital NPT	Monotherapy (n=22)	Polytheraphy (n=17)	p value
DSF	5.77±1.65	5.11±1.45	0.205
DSB	4.50±1.65	3.88±1.93	0.290
CRT.RT	1070±325	1262±431	0.165
CRT.ACC	0.97±0.04	0.93±0.14	0.378
VIS	13.63±5.52	12.05±3.59	0.289
MATRIX	20.13±8.14	17.11±7.70	0.248
DSM	40.18±9.81	35.64±10.98	0.182

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MATRIX: Matrix Reasoning Test, DSM: Digit Symbol Matching

Table 3. Differences between age groups

Digital NPT	<25 years	≥25 years	p value
DSF	5.52±1.83	5.43±1.20	0.873
DSB	4.04±2.07	4.50±1.26	0.439
CRT.RT	1167.56±440.13	1135.83±292.17	0.803
CRT.ACC	0.95±0.12	0.96±0.05	0.724
VIS	13.13±4.92	12.68±4.74	0.781
MAT	20.30±8.21	16.68±7.40	0.168
DSM	38.86±9.54	37.25±11.98	0.640

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

In the group under 25 years of age, there was no significant difference between monotherapy and polytherapy groups in the terms of DSF, DSB, CRT.RT, CRT.ACC, VIS, MAT, DSM tests (p>0.05) (Table 5).

DSB values in the group whose education level is over 12 years; when the groups receiving monotherapy and polytherapy were compared, it was found to be significantly higher in those receiving monotherapy (p<0.027) (Table 6). When this comparison was made between those with an education level of 12 years or less, no significant difference was observed between DNTs (p>0.05) (Table 6).

Table 4. Differences according to education level

Education levels			
Digital NPT	**<12 years**	**>12 years**	**p value**
DSF	4.82±1.38	6.0±1.57	0.02*
DSB	3.70±1.31	4.63±2.01	0.09
CRT.RT	1291.74±415.36	1048.53±325.44	0.047*
CRT.ACC	0.95±0.06	0.95±0.12	0.983
VIS	11.29±3.36	14.22±5.38	0.057
MAT	13.76±6.22	22.72±7.04	0.000*
DSM	34.29±7.66	41.22±11.43	0.030*

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

Table 5. Comparison of digital neuropsychological test subcategories between the groups aged 25 and over and those under 25 who received monotherapy and polytherapy

<25 years			
Digital NPT	**Monotherapy (n=12)**	**Polytheraphy (n=4)**	**p value**
DSF	5.58±1.16	5.0±1.41	0.415
DSB	4.50±1.16	4.50±1.73	0.750
CRT.RT	1043.71±212.36	1412.53±354.60	0.021*
CRT.ACC	0.96±0.04	0.95±0.085	0.834
VIS	12.91±5.29	12.00±2.94	0.854
MAT	18.58±7.37	11.00±4.16	0.078
DSM	39.41±10.75	30.75±14.38	0.225
<25 years			
Digital NPT	**Monotherapy (n=10)**	**Polytheraphy (n=13)**	**p value**
DSF	6.0±2.16	5.15±1.51	0.343
DSB	4.50±2.17	3.69±2.01	0.255
CRT.RT	1103.26±435.87	1217.02±454.48	0.577
CRT.ACC	0.98±0.05	0.93±0.15	0.101
VIS	14.50±5.94	12.07±3.88	0.351
MAT	22.00±9.01	19.00±7.64	0.385
DSM	41.10±9.02	37.15±9.93	0.663

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

Table 6. Comparison of digital neuropsychological test subcategories between groups receiving monotherapy and polytherapy for 12 years or less and over 12 years according to education level

>12 years			
Digital NPT	**Monotherapy (n=12)**	**Polytheraphy (n=10)**	**p value**
DSF	6.25±1.76	5.70±1.33	0.479
DSB	5.33±1.55	3.80±2.25	0.027*
CRT.RT	969.85±223.99	1142.95±409.44	0.356
CRT.ACC	0.98±0.022	0.92±0.18	0.396
VIS	15.66±6.11	12.50±3.97	0.220
MAT	24.33±6.61	20.80±7.40	0.261
DSM	43.50±11.80	38.50±10.94	0.322
≤12 years			
Digital NPT	**Monotherapy (n=10)**	**Polytheraphy (n=7)**	**p value**
FDS	5.20±1.39	4.28±1.25	0.115
DSB	3.50±1.17	4.00±1.52	0.608
CRT.RT	1191.89±395.01	1434.38±430.88	0.172
CRT.ACC	0.96±0.06	0.95±0.06	0.731
VIS	11.20±3.67	11.42±3.15	0.844
MAT	15.10±7.06	11.85±4.59	0.434
DSM	36.20±4.68	31.57±10.43	0.261

*p<0.05.
NPT: Neuropsychological Test, DSF: Digit Span Forward, DSB: Digit Span Backword, CRT.RT: Choice Reaction Time.Reaction Time, CRT.ACC: Choice Reaction Time. Accuracy, VIS: Visual Association Pairs Test, MAT: Matrix Reasoning Test, DSM: Digit Symbol Matching

DISCUSSION

Cognitive impairment is one of the most common complaints in people with epilepsy. This disorder is not only associated with seizures, but may also occur as a side effect of ASDs.[7]

Polytherapy, increased dosage and ASD levels have important roles in this side effect profile. The main disorders detected in cognitive functions are decreased reaction and information processing time with changes affecting memory, attention and language. All these effects may adversely affect drug compliance, tolerability and continuity of treatment during long-term treatment.[8]

Most of the newer ASDs are as effective as the older generation ASDs and appear to be better tolerated overall. The newer ASDs may have less impact on cognitive functions and memory. Neuropsychological testing has been the primary method of objectively examining cognitive function related to the use of ASDs; however, methodological differences in the tests cause contradictions in the results. Changes in cognition may reflect an adverse effect of chronic use of ASDs, but the adverse effects of drugs are only one of several factors that can affect cognition. The new ASDs seem to show little or no adverse cognitive effects.[9] Additionally, many studies have revealed that in-utero exposure to ASD may affect the child's cognitive development in later life.[10]

Our current study has the feature of being the first study in our country in which neuropsychological test evaluation of IGE patients in a digital environment was performed. The reason for choosing IGE patients as the study group is that these patients do not have intellectual disability and focal neurological deficits, and the educational status of 56% of the patients in our study group is over 12 years, providing them with the capacity to perform the current digital operation; Although it can be considered bias, this situation was tried to be prevented by choosing a similar feature in the control group. JME patients constitute a large part of our patient group, and when the literature is searched, notably JME patients constitute the patient group especially in such studies, and it reveals that executive functions are impaired in IGE patients.[11,12] Many studies show that individuals with JME perform worse in attention, mental flexibility, inhibition control, working memory, processing speed, and visual-delayed memory functions compared with healthy individuals.[13,14]

Similarly, in our previous study in which we compared this patient group with healthy controls with DNT subtests, it was found that the DSF, DSB, MAT, DSM and MAT scores of the patient group were lower and the CRT.RT score was higher than the healthy group. This shows that cognitive functionality is worse in attention, short-term memory, working memory, visual memory, episodic memory, cognitive processing speed, selective response/inhibition, fluent cognitive skills, and perceptual reasoning in IGE patients.[15] Although it has been reported in the literature that polytherapy, increased dosage and ASD levels have a significant effect on cognitive function in epilepsy patients, such a difference was not observed in polytherapy users in our current study. It is thought that the fact that the patients frequently use two drugs as polytherapy may be a factor, and the low number of patients in our current sample groups may also have affected the statistical data.

Study Limitations

The weaknesses of our study are that patients with JME constitute a large part of the study, the patient groups that make up the other syndromes of IGE were included in a smaller number in this study, and no information was given about the seizure frequency of the patients. Additionally, the measurement tool we use, DNT McLean Hospital and Harvard University Faculty of Medicine Brain and Cognitive Health Technologies Laboratory, in cooperation with the Many Brains Project, has been made available free of charge only during the COVID-19 pandemic, and tests that include only visual tests in this test battery were applied to patients. Since the verbal tests were in English and all of our patients differed in terms of foreign language knowledge, such tests were excluded from the application. This suggests that there may be a factor in the lack of difference between the groups receiving monotherapy and polytherapy.

CONCLUSION

As a result in our study, which included a limited number of IGE patients, it was concluded that in tests measuring cognitive functions such as executive function, attention, and concentration, the use of a single drug or frequent dual drug use had no effect on the cognitive test success, similarly, age did not affect the results, it seems that the high level of education positively affects the success obtained from the tests.

Ethics

Ethics Committee Approval: The study was conducted following the ethical standards of the Declaration of Helsinki. Marmara University Medical Faculty Clinical Research Ethics Committee approved the study (number: 09.2021.329, date: 09.04.2021).

Informed Consent: All volunteer patients were informed about the study and a voluntary consent form was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., İ.M., Concept: E.A., A.F., G.B.K., C.K., İ.M., Design: E.A., A.F., İ.M., Data Collection or Processing: E.A., A.F., G.B.K., C.K., Analysis or Interpretation: E.A., İ.M., Literature Search: E.A., İ.M., Writing: E.A., İ.M.

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REFERENCES

1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010;51(4):676-685. **[CrossRef]**
2. Devinsky O, Gershengorn J, Brown E, Perrine K, Vazquez B, Luciano D. Frontal functions in juvenile myoclonic epilepsy. Neuropsychiatry *Neuropsychol Behav Neurol*. 1997;10(4):243-246. **[CrossRef]**
3. Roebling R, Scheerer N, Uttner I, Gruber O, Kraft E, Lerche H. Evaluation of cognition, structural, and functional MRI in juvenile myoclonic epilepsy. *Epilepsia*. 2009;50(11):2456-2465. **[CrossRef]**
4. Chawla T, Chaudhry N, Puri V. Cognitive Dysfunction in Juvenile Myoclonic Epilepsy (JME) - A Tertiary Care Center Study. *Ann Indian Acad Neurol*. 2021;24(1):40-50. **[CrossRef]**
5. Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. *Epilepsia*. 1995;36(Suppl 2):S46-65. **[CrossRef]**
6. Passell E, Dillon DG, Baker JT, et al. Digital Cognitive Assessment: Results from the TestMyBrain NIMH Research Domain Criteria (RDoC) Field Test Battery Report. *PsyArXiv*. 2019. **[CrossRef]**
7. Quon RJ, Mazanec MT, Schmidt SS, et al. Antiepileptic drug effects on subjective and objective cognition. *Epilepsy Behav*. 2020;104. **[CrossRef]**
8. García-Peñas JJ, Fournier-Del Castillo MC, Domínguez-Carral J. Epilepsia y cognición: el papel de los fármacos antiepilépticos [Epilepsy and cognition: the role of antiepileptic drugs]. *Rev Neurol*. 2014:24;58(Suppl 1):S37-42. **[CrossRef]**
9. Brunbech L, Sabers A. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: a comparative review of newer versus older agents. *Drugs*. 2002;62(4):593-604. **[CrossRef]**
10. Meador KJ. Cognitive and memory effects of the new antiepileptic drugs. *Epilepsy Research.* 2006;68(1):63-67. **[CrossRef]**
11. Thomas RH, Walsh J, Church C, et al. A comprehensive neuropsychological description of cognition in drug-refractory juvenile myoclonic epilepsy. *Epilepsy Behav*. 2014;36:124-129. **[CrossRef]**
12. Iqbal N, Caswell HL, Hare DJ, Pilkington O, Mercer S, Duncan S. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: a preliminary controlled experimental video-EEG case series. *Epilepsy Behav*. 2009;14(3):516-521. **[CrossRef]**
13. Pascalicchio TF, de Araujo Filho GM, da Silva Noffs MH, et al. Neuropsychological profile of patients with juvenile myoclonic epilepsy: a controlled study of 50 patients. *Epilepsy Behav*. 2007;10(2):263-267. **[CrossRef]**
14. De Toffol B, Van der Linden M, Rolland J. Frontal lobe dysfunction in juvenile myoclonic epilepsy. *Epilepsia.* 1997;38(Suppl 8):S170. **[CrossRef]**
15. Feyzioglu A, Midi I, Ayık E, Kasikci G, Kasikci C. Digital Neuropsychological Assessment of Cognitive Functions in Patients with Epilepsy. *Arch Neuropsychiatry*. 2022. **[CrossRef]**