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Original Article

Cognitive profile of patients with drug-resistant epilepsy based on clinical variability

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Abstract

The present research was conducted with the aim to examine the relationship between clinical variables of epilepsy and cognitive disorders of patients with drug-resistant epilepsy (DRE). From among patients with DRE who had a medical record in Ardabil Welfare Organization, Ardabil, Iran, 35 participants aged between 20 and 35 years old, filled out the questionnaire related to demographic and clinical variables in the summer of 2017. Furthermore, to examine cognitive performance, the Rey-Osterrieth complex figure test and Wisconsin Card Sorting Test were employed. Patients who had emotional turmoil scores higher than 28 (cut-off point) were excluded from the study. Data were analyzed using correlation test and simultaneous regression analysis in SPSS software. The results revealed a significant correlation between clinical variables and cognitive performance. Additionally, based on the obtained regression coefficients, disease duration ($p = 0.35$) did not have a significant role in predicting memory performance. However, seizure frequency ($p = 0.01$), number of anti-epileptic drugs (AEDs) consumed ($p = 0.03$), and age at the onset of seizure ($p = 0.01$) had significant roles in predicting the memory performance. The results also revealed that disease duration ($p = 0.47$), seizure frequency ($p = 0.70$), and age at the onset of seizure ($p = 0.06$) had no significant role in predicting the executive function. Nevertheless, the number of AEDs consumed ($p = 0.02$) had a significant role in predicting the executive function. Clinical factors of epilepsy had a role in predicting cognitive performance of the patients

Keywords

Cognitive function
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Introduction

Drug-resistant epilepsy (DRE) is a multifaceted disorder which is typically the result of the poor management of seizures and is observed in 20% to 40% of all patients with epilepsy (Begley Famulari et al. 2000). Patients with DRE have more cognitive disorders compared to those with drug-responsive epilepsy (López González, Osorio, Gil-Nagel Rein et al., 2015;Valente, Rzezak, Moschetta, 2016).

Cognitive disorders are likely to bear significant impact on the vital performance and daily life of patients with DRE even if the seizure burden is reduced. In practice, it is difficult to recognize and determine the role of all clinical factors affecting cognitive disorders because these variables are often interrelated and occur simultaneously (Mazur-Mosiewicz, Carlson, Hartwick et al., 2015) .Clinical factors affecting the cognitive function of patients with epilepsy are seizure frequency and disease duration (Hermann, Seidenberg, & Bell, 2002), anti-epileptic drugs (AEDs) (Kleen, Scott, Holmes et al., 2013), age at the onset of seizure (Lenck-Santini & Scott, 2015).

There is a correlation between seizure frequency and cognitive disorders in generalized tonic-clonic seizures. Additionally, complex partial seizures are also related to

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the reduction of cognitive function (Thompson & Duncan, 2005). Studies have revealed that, regardless of the type of epilepsy, patients with DRE have weaker cognitive performance compared to those with drug-responsive epilepsy (Smith & Puka, 2016). Repeated seizures in patients with DRE are tightly related to progressive hippocampal atrophy and memory disorders (Alessi, Damasceno, Camargo et al., 2004).

Most of the AED effects are related to attention, consciousness, and mind liquidity reduction. Almost all of these drugs have negative effects on different aspects of cognition depending on type of treatment (single drug or multi-drug treatments) and drug dose. The effect of multi-drug treatment on cognitive function of patients with DRE is still unknown; the number of AEDs, as predictor of patients' attention, executive function, and memory performance (Miller, Galioto, & Tremont, 2016). Previous studies have shown that when the standard dose of AEDs is used, cognitive performance is more satisfactory. For example, single drug treatment with carbamazepine has little effect on cognition. However, in multi-drug treatment with carbamazepine, significant cognitive disorders have been reported (Kwan & Brodie, 2001).

The results of examining the interrelationship of disease duration with age at the onset of seizure (mean age:36 ± 2.54) and memory function in 22 patients with DRE showed that immediate and short-term memory performance in the patients who had the disease for 20 years and more (n = 13) was weaker than those who had the disease for less than 20 years (n = 9). Furthermore, patients who had the disease when they were less than 5 years had weaker performance compared to those who had it after 5 years of age. A longitudinal study on 102 patients with epilepsy and disease duration of 2 to 12 years showed a 50% loss of memory and 28% loss of executive function (Helmstaedter, Kurthen, & Lux, 2003).

Recognizing the mechanisms underlying cognitive disorders among patients with DRE is of great importance due to its significance in determination of cognitive rehabilitation interventions and selection of the cases requiring surgery (Lenck-Santini & Scott, 2015). Since few studies have dealt with the cognitive disorders of patients with DRE in Iran, the present research aimed to examine the interrelationship of seizure frequency, number of AEDs, age at the onset of seizure, and disease duration with the cognitive function of patients.

Method

Participants

The sample of the study consisted of 78 patients with DRE and medical records in Ardabil Welfare Organization, Ardabil, Iran. Among the participants, 24 (68.57%) were male and 11 (31.4%) were female. The majority of them had a diploma (65%) and the rest had an educational degree of less than diploma (35%). In addition, 23 (65.7%) individuals were unemployed and 12 (34.28%) were employed.

Instrument

Demographic Questionnaire

This questionnaire collected data related to Demographic and medical characteristics, including seizure frequency in the past month, type and number of AEDs used, age at onset of seizure, disease duration, time of the last seizure, and seizure duration.

Wisconsin Card Sorting Test (WCST)

In this test, there are 4 sample cards that differ in terms of the shape illustrated on them (rectangle, star, cross, and circle), number of shapes (from one to four shapes), and color of the shapes (green, blue, red, and yellow) and also 60 cards with the same above-mentioned precepts. Each of the cards represents a status that does not repeat. In this test, the participants should insert the cards in one of the sample card categories based on their guessing the precept governing the cards, and then, try to discover the rule governing the categories based on the "true" or "false" feedback they receive. After placing the cards in the correct ten categories, the rule changes and they have to discover the new rule through the same procedure. If the participant follows the categorization based on the previous rule and does not pay attention to the variation of the rule by the experimenter, he/she has committed perseverative error which refers to the repetition of a previously learned precept for a new rule.

Rey-Osterrieth complex figure test (ROCFT)

This test was developed to evaluate the graphic growth, perceptive structuration, and visuospatial memory of participants. It consists of the two A and B cards. In this research study, card A was used which consists of 18 cognitive parts. This test consists of two parts; copy and recall. In the first part, the card is placed at a suitable angle in front of the participant and he/she is asked to copy it on a piece of paper. In the second parts (after three minutes), the participant is asked to draw the previously observed shape without looking at the card. It is scored based on accuracy, correctness, and speed, and also based on all 18 parts of the set (each one has 2 points).

Lvynda Scale

To examine the emotional turmoil of the patients, Lvynda's (1950) scale was used that consists of 21 items which assess stress, anxiety and depression.

Procedure

In this study, Individuals who, in addition to epilepsy, had

mental disability, hemophilia, and severe visual, hearing and mental disorders were excluded from the study. Moreover, considering the effect of emotional turmoil on cognitive performance and its management, patients with emotional turmoil scores of higher than 28 (cut-off point) were also excluded from the study. After telephone calls to the patients, 35 individuals of 20-35 years of age who were willing to participate in the study visited the School of Psychology and Educational Sciences of the University of Mohaghegh Ardabili, Ardabil, Iran. Then, they were asked to response to Demographic Questionnaire , Wisconsin Card Sorting Test (WCST), Rey-Osterrieth complex figure test (ROCFT) and Lvynda Scale individually. The correlation analysis was used to determine the relationship between the clinical variables and cognitive performance. Simultaneous regression analysis was used to evaluate the predictive power of the clinical variables of epilepsy regarding cognitive performance. The data were analyzed by IBM SPSS Statistics, Ver. 20.

Results

Table 1. Mean of clinical variables and cognitive performance in patients with drug-resistant epilepsy

Variable	M (SD)	Range
Seizure frequency (past month)	3.71 (1.31)	**2-6**
Number of anti-epileptic drugs used	3.42 (1.09)	**2-5**
Age at onset of seizure (year)	8.34 (2.70)	**5-12**
Disease duration (year)	18.45 (5.38)	**9-29**
Time of the last seizure (day)	4.05 (2.08)	
Seizure duration (Second)	14.67 (28.44)	
Visuospatial memory	16.40 (2.45)	
Perseverative errors	26.34 (4.88)	

Table 1 presents the mean and standard deviation of epilepsy variables including seizure frequency (3.71 ± 1.31), number of AEDs used (3.42 ± 1.09), age at onset of seizure (8.34 ± 2.70), disease duration (18.45 ± 5.38), time of last seizure (4.05±2.08), and seizure duration (14.67 ± 28.44) and neuropsychological test factors including visuospatial memory (16.40 ± 2.45) perseverative errors (26.34 ± 4.88).

Table 2. The correlation coefficients between clinical variables of epilepsy and cognitive performance in patients with drug-resistant epilepsy

Clinical variable	Visuospatial memory	Perseverative errors
Seizure frequency	-72.0**	**49.0****
Number of anti-epileptic drugs used	-72.0**	**62.0****
Age at onset of seizure	51.0**	**-47.0****
Disease duration	-51.0**	**51.0****

** P < 0.01

The results of the correlation coefficients of clinical variables of epilepsy with visuospatial memory and perseverative error are represented in table 2. A significant correlation was observed between seizure frequency (r = -0.72, r = 0.49), number of AEDs used (-0.72, 0.62), age at onset of seizure (0.51, -0.47), and disease duration (-0.51, 0.51) and visuospatial memory and perseverative error, respectively.

Table 3. The results of regression analysis of clinical variables of epilepsy and visuospatial memory among patients with drug-resistant epilepsy

Predictive variables	B	SE	B	T
Seizure frequency	-0.68	0.27	-0.36	2.49**
Number of anti-epileptic drugs used	-0.72	0.33	-0.32	2.17*
Age at onset of disease	0.26	0.10	0.30	2.50*
Disease duration	-0.50	0.58	-0.11	-0.93

Note. B: unstandardized coefficient; SE: standard error; β: standardized coefficient
*P < 0.05, **P < 0.01

The results of simultaneous regression analysis showed that 69% of variance in total score of visuospatial memory (F= 17.25; P<0.001) was explained by the clinical variables of epilepsy. Moreover, the closer study of regression analysis showed that the standard regression coefficient of seizure frequency (t = 2.49; P < 0.010), number of AEDs (t = 2.17; P < 0.030), and age at onset of disease (t = 2.50; P< 0.01) was significant in predicting visuospatial memory. The disease duration could not predict visuospatial memory (t = -0.93; P< 0.350) (Table 3).

Table 4. The results of simultaneous regression analysis of clinical variables of epilepsy and perseverative error in patients with drug-resistant epilepsy

Predictive variables	B	SE	B	T
Seizure frequency	0.26	0.69	0.07	0.38
Number of anti-epileptic drugs used	2.03	0.83	0.45	2.44*
Age at onset of disease	-0.52	0.26	-0.29	1.94
Disease duration	0.10	0.14	0.11	0.73

Note. B: unstandardized coefficient; SE: standard or; β: standardized coefficient $^{*}P < 0.05$ $^{**}P < 0.01$

The results of simultaneous regression analysis illustrated that 51% of variance in total score of perseverative error ($f = 7.06$; $P < 0.001$) was explained by the clinical variables of epilepsy. Moreover, the closer examination of regression analysis showed that the standard regression coefficient of seizure frequency ($t = 0.38$; $P < 0.020$), age at onset of disease ($t = 1.94$; $P < 0.060$), and disease duration ($t = 0.73$; $P < 0.470$) was not significant in predicting perseverative error. The standard regression coefficient of number of AEDs was significant in predicting perseverative error ($t = 2.44$; $P < 0.020$) (Table 4).

Discussion

The present research aimed to shed light on the relationship between clinical variables of epilepsy and neuropsychological function of patients with DRE. Different related studies have supported the incidence of brain function disorder in these patients (van Rijckevorsel, 2006) The results of the current study revealed that seizure frequency (-0.72), number of AEDs (-0.72), age at onset of seizure (0.51), and disease duration (-0.51) are correlated with visuospatial memory. Moreover, 69% of the whole variance in visuospatial memory is accounted for by these clinical factors ($F = 17.25$, $P \leq 0.001$), and among the studied variables, disease duration had no significant role in predicting visuospatial memory. Additionally, seizure frequency (0.49), number of AEDs consumed (0.62), age at onset of seizure (-0.47) and disease duration (0.51) had significant correlations with perseverative error. Furthermore, 51% of the whole variance in perseverative error is accounted for by these clinical factors ($F = 7.06$, $P \leq 0.001$). Among these clinical factors, the number of AEDs had a stronger role in the prediction of perseverative error compared ot other variables. The studies revealed a significant relationship between seizure frequency and memory function (Alessio & et al, 2004; Hendriks & et al, 2004; Wang & et al, 2011). Accordingly, maximum control of seizure frequency to reduce the risks and consequences of epilepsy is of great importance as some related studies have proved the predictive role of seizure frequency regarding patients' memory function (Voltzenlogel & et al, 2015). Often the structural cause of hippocampal sclerosis (HS) is under consideration in this regard (Schwarz & et al, 2004). Examinations on 12 patients with unilateral temporal lobe epilepsy have shown the relationship of progressive atrophy and memory defects with repeated seizures (Fuerst & et al, 2003).

In patients with unilateral temporal lobe epilepsy, seizure frequency had a predictive role regarding executive function (Wang & et al, 2011). Lah's study also revealed that the number of AEDs was a predictor of memory function and there was a negative correlation between the number of AEDs and episodic memory function of the patients (Lah & et al, 2006). The reason the clinical variables of epilepsy are the best predictors of neuropsychological functions in patients with epilepsy is not exactly known (Miller & et al, 2016). Seizure in patients with DRE might be the consequence of severe brain process (Cendes & et al, 2014). Anatomical aberrations of cognitive disorders among patients with epilepsy including uncinate fasciculus (part of the white substance between temporal and parietal lobe) are related to reduction in memory function. Similarly, the size of corpus callosum and the integrity of frontostriatal circuits are related to defects in executive function of the patients (Riley & et al, 2010). Reduction of gray matter in the parietal and occipital left lobes leads to decreased cognitive function in patients with epilepsy (Hermann & et al, 2006). In other words, the nature of epilepsy may be the cause of cognitive disorders in patients.

In addition to the fixed defect of brain disorders, patients with epilepsy also experience dynamic changes related to interictal discharges and undesirable effects of AEDs (Mohanraj, 2015). Regarding AEDs and their effects on cognition, dose of drugs and multidrug treatment are important factors (Eddy & et al, 2011). Considerable improvement of cognitive function has been reported as a result of decreasing the dose of AEDs and omitting one or two drugs among patients with DRE who were simultaneously undergoing perampanel (PER) treatment (Vecht & et al, 2017). The role of AEDs in cognitive disorders is complicated and contradictory and is not necessarily only negative. These drugs reduce the seizure frequency through reducing the activity and excessive shooting of neurons which, in turn, balance neurotransmitters and Control cellular functions related to

Ca^{2+}, but other mechanisms also occur (Tang & et al, 2007). Generally, the detrimental impact of AEDs on cognition might be due to obstruction of the Na^{+} canal, increase in gamma-aminobutyric acid (GABAergic) activity, and decrease in stimulations resulting from patients with DRE who suffered from the disorder from childhood showed more memory disorders. Seizures which occur during childhood have negative effects on the natural integrity of neurons and lead to more functional and structural damages, especially in temporal lobe epilepsy (Hamed, 2009).

One of the limitations of the present research was the lack of access to the specific damaged area of the brain and lack of access to functional magnetic resonance imaging (fMRI) and pharmaco magnetic resonance imaging (ph-MRI) for the determination of the exact areas of the brain involved in cognitive functions and possibly affected by the drugs. Through the recognition of the area of damage and type of epilepsy more detailed information can be obtained regarding the cognitive disorders of patients. Another limitation of the study was its small sample volume which was related to the attempt to have a homogeneous sample of patients and to observe the ethical principle of patients' willingness to participate in the study. The results of the present study showed that the number of AEDs used had a significant effect on the cognitive function of patients with DRE. Thus, further studies are recommended to examine and discover the best possible drug combination with the least possible impact on the cognitive function of patients with DRE. Moreover, to reach more precise findings, the use of a more homogeneous and controlled sample and a larger sample volume are suggested.

Conclusion

Physicians usually encounter a set of cognitive challenges and problems while dealing with epilepsy, and the issue of cognitive disorder in patients with epilepsy is still a challenging issue for them. Poor control and increasing frequency of seizures in patients with DRE are often accompanied by a greater reduction in cognitive function. Determining cognitive dimensions in patients with DRE allows physicians to make use of more effective and comprehensive treatment strategies to better manage their disorders. Therefore, it is necessary to take into consideration all clinical factors of epilepsy when studying the neuropsychological function of patients with epilepsy so that success can be achieved in the selection of an effective cognitive rehabilitation treatment strategy and surgery.

Conflict of interest

The authors this article declare that there was no conflict in interest.

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