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Executive functions in migraineurs

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Abstract

Objective: To investigate whether there is an impairment in executive functions, which are among the frontal lobe functions, in interictal periods of migraine patients and hence to determine whether there is a neuropyschological pathology in the frontal lobe. *Methods:* Fifty-seven patients who presented to our neurology outpatient clinic and were diagnosed with migraine and 57 healthy controls were included in this prospective study. Neuropsychological tests evaluating executive functions were administered to migraine patients in the interictal period, and the results were compared among the migraine patients themselves and between the migraine and control groups. *Results:* Cases with migraine completed the Stroop test in significantly longer times and with more mistakes than controls. They could produce a lower number of words starting with the letters K, A, and S. The control group explained and interpreted proverbs better than did the migraine group. There was a significant difference between cases who had migraine for five or fewer years and those who had migraine for six years or more in terms of mini mental test scores, Stroop 5 duration, Stroop 5 mistake scores, and categorical fluency scores, while there was no difference in terms of other tests.
Conclusion: Migraine is a disease that causes impairment in executive functions and skill of programming behavior and leads to impairment in the frontal regions of the brain. Therefore, treatment aiming to prevent migraine attacks may contribute significantly to the protection of the brain and its functions.

Keywords: Migraine, cognition, executive functions

INTRODUCTION

Migraine is the most common disabling neurological disease throughout the world.[1] A common brain disorder with high disability rates, migraine involves a series of abnormal neuronal networks interacting at different levels of the central and peripheral nervous system.[2] It has been demonstrated that migraine patients complain of cognitive dysfunctions, which mainly involve attention and memory, during attacks.[3-5]

However, there is conflicting data on whether cognitive dysfunction is present in the interictal period. There are few studies investigating the cognitive performance of migraine patients. While some clinical studies have demonstrated cognitive dysfunction, these results could not be corroborated in population-based studies.[6]

Cognitive dysfunction in migraine patients involves delayed visual memory, decrease in comprehensive intelligence, and impairment in executive functions, all of which become more evident during migraine attacks. Executive functions are a number of high-level functions that serve to facilitate adaptation to new and complex situations in which present cognitive skills and behaviors are not sufficient. They include reasoning, planning, problem solving, and mental skills that help to conduct one's life.[7]

Although many of our daily activities can be conducted routinely, in some situations, the intervention of control mechanisms is required for producing suitable and effective performance.[8] These are functions based upon maintaining attention. When executive functions are impaired, it becomes difficult to maintain attention, perseverations may occur, one can easily be distracted, resistance against interference decreases, and the suppression of sudden and unsuitable reactions becomes more challenging.[9] There are findings suggesting that executive functions are impaired in frontal lobe lesions.[10] In the presence of impairment in executive functions, behavioral disturbances, such as improper sexual behavior and changes in temperament, and other problems, such as being easily distracted and experiencing difficulty in abstraction, may arise.[11] It is known that in migraine patients, there is impairment in executive functions, which are associated with frontal lobe.[12]

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The aim of the present study was to investigate whether there is an impairment in executive functions, which are among the frontal lobe functions, in the interictal period in migraine patients and hence to determine whether there is a neuropsychological pathology in the frontal lobe.

METHODS

This study was planned and done as a sectional case-control study. The patient group consisted of people aged 20-63 who randomly applied to the outpatient clinic of Ankara Numune Training and Research Hospital within a 3 months period and met the inclusion criteria specified for the study. The patient group included 57 patients (50 females, 7 males). The control group included 57 age and sex matched healthy subjects (44 females, 13 males) between the ages of 20 and 62 who did not have a diagnosis of migraine. Our study was approved by the local ethics committee of our medical center.

The inclusion criteria was patients diagnosed with migraine according to the diagnostic criteria of the International Headache Society (HIS); and male and female patients over the age of 20 years. The healthy volunteers not diagnosed with migraine and matched with patients for age and sex were included in the control group. The exclusion criteria for both case and control were: Not completed at least five years of schooling; those with mental retardation, a history of epilepsy (who used or did not use drugs), demyelinating disease, hypothyroidism, or color blindness.

The results of the neuropsychological tests administered to migraine patients in the interictal period to evaluate executive functions were compared among the patients and with the control group. All patients underwent evaluation with a visual analog scale (VAS). In order to assess the effect of migraine on the patients' daily activities, the migraine disability assessment scale (MIDAS) was used.

Neuropsychological battery

The neuropsychological battery performed were:
Mini mental state examination (MMSE);
Tests evaluating executive functions: Stroop test;
Word fluency: Category fluency (Animal), Phonemic fluency (K-A-S);
Abstract thinking: Binary similarities, Interpretation of proverbs.

Statistical analysis

To analyze the data obtained from the participants, parametric analysis was performed using SPSS 17.00. To determine whether there was a difference in measurements made between the two groups forming the sample, the t-test was used, and the Pearson correlation method was employed to investigate the relation between different measurements. In only the patients group, Mann-Whitney U analysis was performed to determine whether there was a difference in parameters associated with the disease.

RESULTS

Overall, 114 subjects (57 migraine patients and 57 healthy controls) were included in the present study. Patient and control groups were similar in terms of mean age (X=37,579, p<0 .05), sex (X=2.183, P <0.05), education status (X=1,791, p<0.05) and hand preference (Table 1). A large majority of migraine cases (96.5%) had migraine without aura. Table 2 contains the data regarding frequency of headache attacks and total duration of the disease.

A strongly significant positive correlation was found between the ages of migraine patients and their durations for Stroop parts 1, 2, 3, 4, and 5 and mistake scores for Stroop part 5. Accordingly, duration of Stroop and mistakes in Stroop 5 increased as age increased. In addition, a significant negative correlation was found between age and MMSE scores, category fluency scores, and scores of words produced beginning with the letter S and overall (with the letters K, A, and S). However, there was no significant correlation between age and the other scores (Table 3).

In migraine patients, a significant positive correlation between overall duration of migraine and Stroop 5 mistake scores, without any correlation with the other parts of the test, was established. The rate of mistakes in Stroop 5 increased as the duration of migraine disease increased (Table 3).

A significant positive correlation was found between the frequency of migraine attacks and the duration of Stroop 4, and a negative correlation was found between the frequency of attacks and the category fluency scores; the production of words starting with letters A, K, and S and overall the binary similarity scores; and the proverb interpretation scores. However, no correlation was found between frequency of attacks and the other scores (Table 3). In the evaluation of the correlation between VAS (visual analog scale)

Table 1. Sociodemographic characteristics of the groups

Demographic characteristics	Migraine patients (N=57)		Control (N=57)		Overall (N=114)	
Sex	**N**	**%**	N	%	N	%
Female	50	87.7	44	77.2	94	82.5
Male	7	12.3	13	22.8	20	17.5
Education						
Primary school	26	45.6	23	40.4	49	43
Secondary school	6	10.5	10	17.5	16	14
High school	11	19.3	8	14.0	19	16.7
University	14	24.6	16	28.1	30	26.3
Occupation						
Unemployed/housewife	26	45.6	19	33.3	45	39.5
Public servant	16	28.1	16	28.1	32	28.1
Workers	8	14	19	33.3	27	23.7
Free enterprise	4	7	2	3.5	6	5.3
Retired	3	5.3	1	1.8	4	3.5
Hand preference						
Right	53	93	53	93	106	93
Left	4	7	4	7	8	7
	Mean	**SD**	**Mean**	**SD**		
Age	34.75	9.09	35.49	10.04		

scores and neuropsycological battery scores in migraine patients, no significant association was found (Table 3).

A significant negative correlation was found only between MIDAS scores and the score of producing words starting with the letter K, without any correlation with the other scores. Accordingly, as MIDAS scores increased, the number of words produced starting with the letter K decreased (Table 3). No significant difference was found between patients and control groups with respect to MMSE scores ($p = 0.051$). Additionally, no significant difference was found between groups in terms of mean duration of the Stroop test and its parts ($p < 0.05$).

The number of mistakes made in part 5 of the Stroop test was found to be significantly higher in the patient group than the control group, while there was no significant difference in the number of mistakes made in other parts of the test. A significant difference was found between migraine and control groups with respect to category fluency test scores; that is, migraine patients remembered a lower number of words than the control group. There was a significant difference between migraine and control groups in the word fluency test, with the migraine patients remembering a lower number of words starting with the letters

Table 2: Type of migraine, frequency of attacks, and total duration of disease

Migraine type	N	%
With aura	2	3.5
Without aura	55	96.5
	Mean	**SD**
Frequency of migraine attacks	5.37/month	3.7
Duration of migraine disease	8.16/years	6.17

Table 3. Correlation findings between age, migraine onset age, migraine attack frequency, and scales applied with VAS and MIDAS in migraineurs

Scales	Age	Migraine onset age	Migraine attack frequency	VAS	MIDAS
	r coeffient	r	r	r	r
Mini Mental	**-.273***	-.207	-.163	-.237	-.243
Stroop1 duration	**.370****	.145	.162	-.129	.136
Stroop1 mistake	-.002	.032	-.109	-.030	.102
Stroop2 duration	**.480****	.160	.165	-.005	.090
Stroop2 mistake	.252	.035	.021	.069	.015
Stroop3 duration	**.422****	.177	.178	-.051	.078
Stroop3 mistake	.172	.067	.068	.034	-.086
Stroop4 duration	**.416****	.210	**.306***	-.015	.110
Stroop4 mistake	.098	-.070	.116	.039	.015
Stroop5 duration	**.384****	.217	.063	.022	.161
Stroop5 mistake	**.401****	**.292***	.087	.041	.246
Category	**-.299***	-.173	**.379****	-.064	-.260
Letter K	-.220	-.008	**.389****	.035	**-.271***
Letter A	-.231	-.140	**-.322***	-.035	-.166
Letter S	**.279***	-.043	**-.306***	.003	-.212
Overall KAS	**-.266***	-.066	**-.372****	.003	-.240
Similarity	-.122	-.136	**-.405****	-.034	-.067
Proverb	-.034	-.014	**-.332***	-.018	-.086

(Pearson's Correlation Test)
*p<.05, **p<.01

S, K, and A. It was also found that the migraine patients interpreted a lower number of proverbs correctly than the control group (Table 4).

DISCUSSION

Zeitlin and Oddy first demonstrated that a significant decrease in performance was observed in memory and information processing tests in a group of patients with severe migraine.[12] Similarly, Hooker and Raskin reported that compared to controls, migraine cases complained more from cognitive dysfunction, and there was a decrease in their neuropsychological test performance.[13]

Martins *et al*. observed worse performance in migraine patients in attention and processing speed tests.[14] In addition, Pellegrino *et al*. established impairment in executive functions in their migraine subject.[15]

However, in 1987, Sinforiani *et al*. could not demonstrate the presence of cognitive dysfunction in a group of migraine patients with or without aura.[16] Consistent with the above study, Leijdekkers *et al*., in their study on a group of women with migraine, reported no cognitive impairment in migraine cases.[17] Likewise, in a study by Jelicic *et al*. and in a population-based study by Gaist et al., cognitive scores were found to be similar between migraine and other groups.[18,19]

In the present study, in view of such conflicting data, we investigated whether there was impairment in executive functions, which mostly reflected frontal lobe functions, in the interictal period. The most commonly reported cognitive dysfunctions in migraine patients are delayed visual memory[20-22] and decrease in detailed intelligence[23] and executive functions.[20-24] All of these problems are more evident during migraine attacks, while in the intervals between attacks, i.e., in the interictal periods, they also continue to impair cognitive functions.[25] Considering that headache during migraine

Table 4. T-test results for Mini Mental State Examination, Stroop, KAS, Similarity and Proverb test scores

SCALES	T	P
MMS	-1.972	0.051
Stroop1 duration	3.292**	0.001
Stroop2 duration	3.251**	0.002
Stroop2 mistake	2.511	0.013
Stroop3 duration	3.697***	<0.001
Stroop3 mistake	0.305	0.761
Stroop4duration	4.286***	<0.001
Stroop4 mistake	0.212	0.833
Stroop5 duration	4.411***	<0.001
Stroop5 mistake	3.970***	<0.001
Category	-3.402**	<0.001
Letter K	-3.616***	<0.001
Letter A	-3.681***	<0.001
Letter S	-3.745*	<0.001
Overall K,A,S	-3.896***	<0.001
Similarity	-4.120***	<0.001
Proverb	-2.603*	0.01

attacks and accompanying symptoms may affect neuropsychological performance, we chose to evaluate our patients in the period between attacks to determine whether the adverse effects of migraine on executive functions are still present in the interictal period. The prevalence of migraine has been reported to be three times as common in women as in men[26], and in our present study of randomly selected cases, males accounted for 12% of cases, and females, 88%. As education level may influence the adaptation of cases to cognitive challenges, care was taken to distribute this parameter evenly between the migraine and control groups. Both groups underwent a MMSE, and no significant difference was found between groups in terms of test scores; that is, a global evaluation of mental status yielded comparable results.

It has been demonstrated that executive functions are affected more by diffuse frontal lobe lesions than by focal lesions.[8] Ischemia that can arise during migraine attacks in association with the hours-long decrease in cerebral blood flow may lead to changes in brain gray matter.[27] In a study by Rocca *et al*. using voxel-based morphometry, in migraine patients with hyperintense lesions visible in T2 sections, gray matter density in various brain regions was shown to be significantly decreased compared to the control group. They also reported that these changes were bilateral and were located especially in the frontal and temporal lobe cortexes and cingulum.[28] Therefore, these findings suggest that long-lasting cerebral oligemia lead to diffuse rather than focal pathology, giving rise to impairment of executive functions.

In the present study, patients and control groups were administered the Stroop test, which is a neuropsychological test reflecting frontal region activity. As mentioned above, performance on the Stroop test mirrors the degree of cognitive rigidity/flexibility in the individual. These functions are mainly involved with the frontal lobe activities of the brain. In fact, excessive impairment in such functions and general behavior programming capacity directly point to a problem particularly in the frontal lobe.[29]

In our study, it took significantly longer for migraine patients than control to complete the Stroop test, and they made significantly more mistakes in Stroop part 5. Based on these, it was thought that attention skill in migraine patients was more impaired than control. In a study by Annovazzi *et al*. including 13 migraine patients and 13 control cases, it was reported that there was significant slowing in reaction times of migraine patients on the Stroop test.[30] In a study by Schmitz *et al*., although no difference was found between migraine and control groups with respect to Stroop test scores, in migraine patients, a significant decrease was shown in middle

frontal gyrus gray matter density, which is one of the most significant brain regions for executive functions. Moreover, it was also reported that in migraine patients with lower frontal gray matter density, reaction and response time was longer in some tests, such as the set-shifting test.[25] We also used tests evaluating word fluency and abstract thinking. It was established that migraine cases could produce a lower number of words starting with letters K, A, and S, with a statistically significant difference. According to these results, it was thought that word association skill performed poorer in the migraine patients than control . In the abstract thinking, when binary similarity scores were evaluated, lower scores in the migraine patients suggested that migraine reduced abstract and verbal logical thinking capacity. As to the interpretation of proverbs, the higher number of correct answers in the control group indicated that judgment skill was superior in the control group.

When migraine cases were compared with each other with respect to age, neuropsychological tests, and MMSE scores, it was found that with increasing age, Stroop test completion took more time, the rate of mistakes in Stroop part 5 increased, and there was drop in MMSE and category fluency test scores. These findings indicated that there was a decrease in cognitive functions with age in migraine cases, but they were discrepant with the findings of Jelicic *et al*. and Baars *et al*., who reported that age exerted no significant impact on cognitive functions in migraine patients. In a case-controlled study by Camarda *et al*. evaluating executive functions in 45 migraine patients without aura, it was found that their test performances were lower than those of the control group and that mild executive function impairment was present even in the interictal period.[18,31,32] In the evaluation of the correlation between frequency of migraine attacks and executive functions, our study found that as the frequency of attacks increased, completing Stroop part 4 took more time, and category fluency scores, the number of words produced starting with the letters K, A, and S and overall, binary similarity scores, and proverb interpretation scores decreased. In addition, with increased frequency of migraine attacks, executive functions became more impaired. In a study by Camarda *et al*. that obtained similar results to our study, it was proposed that this dysfunction may be associated with the cumulative effect of recurrent migraine attacks on the prefronto-cerebellar loop.[32]

To investigate the effect of chronic migraine on executive functions, we evaluated the relation between total duration of migraine disease and the neuropsychological tests patients underwent. We found significant differences between cases with a migraine history of five years or less and those with a migraine history of six years or more with respect to MMSE scores, Stroop 5 duration, Stroop 5 mistake scores, and category fluency scores, while no significant difference was found in the other tests. According to these results, in cases with a migraine history of five years or less, MMSE scores were higher than in the other group. Similarly, those with a migraine history of five years or less completed the Stroop 5 test in a shorter time and made a lower number of mistakes. In the category fluency test, they also remembered more words than migraine cases of six years or more; that is, it was established that migraine cases of five years or less were able to maintain their attention under distraction, remembered more words, and had better cognitive functions. In view of these data, it was concluded that longer duration of migraine disease exerted a negative impact on cognitive and executive functions. However, in studies by Bell *et al*., and Le Pira *et al*., no correlation was demonstrated between duration of disease and cognitive deficit.[33,17] Similarly, Pearson *et al*. reported that cognitive function was preserved in migraine cases in spite of long-term disease.[34] We investigated whether there was a correlation between the severity of migraine attacks and migraine-associated disability and executive functions. For this purpose, VAS scores, used in measuring the severity of attacks, were compared with MIDAS scores and neuropsychological test scores. No correlation was found with VAS scores, while the number of words produced starting with the letter K decreased as MIDAS scores increased. Accordingly, the severity of migraine attacks exerted no unfavorable effect on executive functions, at least in the interictal period. These findings may also be interpreted as follows: a correlation with severity could not have been demonstrated, as tests were not administered during attacks. In addition, the severity of pain may be subjective, as pain perception varies from person to person.

According to the results of our study, maintaining attention under distracting conditions, which is one of the executive functions of the frontal lobe, is impaired in migraine subjects. In addition, abstract and verbal logical thinking and judgment skill also decrease in migraine patients. There is a decrease in cognitive functions in

migraine patients with advancing age. As the frequency of migraine attacks increases, there is more marked impairment in executive functions. Longer duration of migraine history exerts a negative impact on cognitive and executive functions. The severity of migraine attacks exerts no negative impact on executive functions in the interictal period.

In conclusion, migraine may cause impairment in executive functions and behavior-programming skills with dysfunction in the prefrontal regions of the brain. As the frequency of migraine attacks increases, impairment is observed in executive functions, so preventive treatments to prevent migraine attacks may be important in protecting the brain and its functions.

DISCLOSURE

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