DOES CONSTIPATION HAVE AN EFFECT ON COGNITIVE FUNCTIONS? A PROSPECTIVE CLINICAL STUDY

Kabızlığın Kognitif Fonksiyonlar Üzerine Etkisi Var Mı? Prospektif Klinik Bir Çalışma

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of constipation on cognitive functions.

Material and Methods: The study was designed prospectively. Patients diagnosed with constipation were included in the study group, while individuals without any complaints comprised the control group. Patients' demographic characteristics, including age, gender, and education level, were evaluated. All participants of the study underwent Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Montreal Cognitive Assessment (MoCA) test, Digit Span Memory (DSM) test and Stroop test.

Results: The patient and control groups consisted of 60 (mean age: 36.81±6.88 years) and 59 individuals (mean age: 36.1±10.2 years) respectively. There was no significant difference between the two groups in terms of demographic characteristics ($p>0.05$). The BAI and BDI scores were significantly higher in the patient group ($p<0.05$). In addition, the MoCA subcomponents (such as executive function, attention, language abilities, and delayed recall), the total MoCA score and the DSM scores were significantly lower in the patient group ($p<0.05$). Finally, five subcategories from the Stroop test were significantly higher in the patient group ($p<0.05$).

Conclusion: In addition to the fact that anxiety and depression are higher in patients with constipation compared to healthy controls, it is revealed that cognitive functions are also negatively affected by constipation, thus suggesting that clinical constipation should not be underestimated.

Keywords: *Constipation; Cognitive İmpairment; Depression; Anxiety*

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ÖZET

Amaç: Bu çalışmadaki amacımız, kabızlığın kognitif fonksiyonlar üzerine etkisinin olup olmadığını araştırmaktı.

Gereç ve Yöntemler: Çalışma, prospektif olan dizayn edildi. Kabızlığı olduğu belirlenenler hasta grubu olarak, herhangi bir şikayeti olmayanlar ise kontrol grubu olarak çalışmaya dahil edildi. Her iki grubun yaş, cinsiyet ve eğitim süresini içeren demografik özellikleri değerlendirildi. Ayrıca çalışmaya dahil edilen tüm gönüllülere Beck Depresyon Envanteri, Beck Anksiyete Envanteri, Montreal Kognitif Değerlendirme Testi(MoCA), İleri ve Geri Sayı Menzili Testi ve Stroop Testi uygulandı.

Bulgular: Sağlıklı kontrollere kıyasla kabızlığı olanlarda anksiyete ve depresyonun daha yüksek görülmesinin yanı sıra, kognitif fonksiyonların da kabızlıktan olumsuz etkilendiğinin belirlenmesi, klinik açıdan kabızlığın hiçte hafife alınmaması gerektiğini ortaya çıkarmaktadır.

Sonuç: Hasta grubu 60 (ortalama yaş: 36.81±6.88), kontrol grubu (ortalama yaş:36.1±10.2) ise 59 gönüllüden oluşturuldu. Her iki grup arasında demografik özellikleri açısından anlamlı fark yoktu($p>0.05$). Beck Anksiyete ve Beck Depresyon ölçek puanı hasta grubunda anlamlı derecede yüksek(sırasıyla $p=0.037$, $p=0.004$) bulunurken; MoCA alt bileşenlerinden yönetici işlevi, dikkat, lisan ve gecikmeli hatırlatma hasta grubunda anlamlı derecede düşük bulundu($p<0.05$). Toplam MoCA puanı da olgu grubunda anlamlı derecede düşük bulunmuştur($p<0.001$). Öte yandan ileri, geri ve toplam sayı menzil puanı hasta grubunda anlamlı derecede düşük bulunmuştur($p<0.001$). Stroop 5 süre değeri hasta grubunda anlamlı derecede yüksek($p=0.024$) tespit edilirken, testteki diğer bileşenlerde iki grup arasında anlamlı fark saptanmamıştır($p>0.05$).

Anahtar Kelimeler: *Kabızlık; Kognitif Bozukluk; Depresyon; Anksiyete*

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INTRODUCTION

Constipation is a common gastrointestinal system complaint, and its prevalence has been reported to be around 44% (1). Etiologic factors are various like diabetes, renal insufficiency, hypothyroidy and some medications (opioids and anticholinergics) (2).

Patients with constipation may experience nausea, vomiting, abdominal pain, bloating, and cramps or even rectal prolapse, hemorrhoidal disease, and anal fissures, may occur. In addition to these gastrointestinal system-related problems, it has been shown that constipation also affects the genitourinary and endocrine systems (3). The emergence of such problems may cause a negative impact on the daily activities and also lead to decreased work efficiency. Some studies have shown poor health-related quality of life in patients with constipation (4,5).

In addition, some patients with constipation may develop psychological disorders, including somatization, obsessive-compulsive disorder, depression, anxiety, and psychoticism (6). All these psychological problems can lead to social isolation. One study showed that cognitive impairment was significantly higher in patients with depressive disorder compared to healthy subjects (7). In fact, in a study of 664 people with depressive disorder, approximately 75% of these individuals had at least one cognitive dysfunction (8). Thus, it can be predicted that constipation adversely affects cognitive functions by causing deterioration of daily living activities and development of various psychological disorders, including depressive disorders.

In recent years, the enteric nervous system (ENS) has been described as a second brain because of its similarity with the central nervous system (CNS). Nearly every class of neurotransmitters found in the CNS has also been detected in the ENS (9). Moreover, developments of both the ENS and CNS have been reported to be highly parallel (10). Therefore, environmental and genetic factors that affect the development and function of the CNS may also affect the development and function of the ENS. Furthermore, intestinal functions are thought to be specifically linked to the emotional and cognitive centres of the brain (11). This linkage regulates homeostatic functions that are classically thought to be predominantly gut- and brain-centred. While these homeostatic functions include sensory and motor functions in the intestine, they develop around the control of cognitive, behavioural, and mental health in the CNS. In other words, an abnormal condition that occurs in any of these systems may lead to a disease that affects both systems. Based on this information, we think that constipation may have a negative effect on cognitive functions.

In the literature, there are a limited number of studies which compared cognitive functions of patients with constipation and healthy subjects. In this study, we aim to address this issue.

MATERIAL AND METHODS

The study was conducted in general surgery and neurology clinics in accordance with the 1975 Declaration of Helsinki. Our study was performed prospectively. Signed informed consent forms were obtained from all participants.

Individuals who appealed to general surgery clinic due to constipation lasting for at least 6 months and who did not have any organic pathology that may cause constipation were evaluated. Constipation was diagnosed according to the patient's complaints; that is a patient with infrequent defecation and hard faeces. The Rome III constipation criteria were used to diagnose patients with irritable bowel syndrome and those patients were excluded (12). A total of 60 patients between the ages of 18- 55 years that did not have any psychiatric diseases, had no history of psychiatric drug use, and were willing to participate in the study were included in the study as a patient group. Fifty-nine healthy volunteers who had similar demographic characteristics, had no health-related complaints or psychiatric diseases, and had no history of psychiatric drug use were included in the study as a control group. All participants of the study filled out the form that included information on age, sex and education level.

A neurologist performed The Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Montreal Cognitive Assessment (MoCA) test, Digit Span Memory (DSM) test and Stroop test on all participants of the study. The purpose of the BAI is to determine the frequency of anxiety symptoms experienced by individuals. It was developed by Beck et al.

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in 1988 and is used as a Likert-type self-assessment scale (13). The higher the total score is, the higher the anxiety experienced by the person.

The BDI was developed by Aaron T. Beck et al. in 1961 to measure cognitive, emotional, and motivational trends in depression (14). The aim of the scale is not to diagnose depression but to objectively quantify the degree of its symptoms. A high total score indicates the severity of depression.

The MoCA test was developed as a screening test to assess mild cognitive impairment. Various cognitive functions, such as memory, visual-spatial skills, executive functions, verbal fluency and abstract thinking, attention, concentration and working memory, language, time, and location orientation are evaluated in this test. It is developed by Nasreddine et al and very easy to use in evaluating the cognitive functions (15).

The DSM test is the most commonly used attention/short-term memory test. The test consists of two parts. In the beginning, the person is asked to repeat the numbers told to her/him in the same order, and then asked to repeat the numbers from last to first. For both parts of the test, the span right before two incorrect calls in succession was recorded as a result (16).

The Stroop test is a neuropsychological test that reflects the frontal region activities of the brain (17). The original test developed by Stroop in 1935 and its various types are used to evaluate attention. This test can evaluate the ease of changing the perception target or perceptual setup in line with changing demands, the ability to suppress a habitual behaviour pattern, the ability to conduct unusual behaviour, speed of information processing, and automatic and parallel processing in cognitive processes.

Statistical Analyses

SPSS 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) was used for statistical analysis of the data. The Kolmogorov-Smirnov test was used to assess the normality of distribution. The Chi-square test was used to compare categorical variables. The Student-t test was used for comparison of two groups in the data showing normal distribution, and the Mann-Whitney U was applied for non-normally distributed variables. The Pearson correlation test was used for correlation analysis of normally distributed data, while the Spearman correlation test was used for non-normally distributed data. A p value of less than 0.05 was considered statistically significant.

Ethics Committee Approval: Ethics committee approval was received for this study from local Clinical Research Ethics Committee (Decision Date: 29.05.2019; Decision No: 2017-KAEK-189_2019.05.29_18)

RESULTS

There was no significant difference between the patient group and the control group in terms of age, gender and education level (p = 0.672, p = 0.792, p = 0.204, respectively). The sociodemographic characteristics of the groups are shown in Table 1.

The BAI scores of the patient group were significantly higher compared to the control group (p= 0.037). Similarly, the BDI scores were also significantly higher in the patient group (p= 0.004). There was no significant difference between the two groups in terms of naming, abstract thinking and orientation scores of the MoCA subcomponents (p > 0.05). However, attention, executive functions, and delayed recall scores of the MoCA subcomponents were significantly lower in the patient group (p < 0.001). Similarly, the

Table 1: Sociodemographic Characteristics

	Patient group n=60	Control group n=59	*p* value
Age*	36.81 ± 6.88	36. 1 ± 10.2	0.672‡
Gender: Female (%)	36 (60)	33 (55.9)	0.792§
Education Level (year) †	8 (5-20)	8 (5-17)	0.204‖

*Data were shown as mean ± standard deviation. †Data were shown as median (min-max). ‡p-values were calculated by the independent t-test. §p-values were calculated by the chi-square test. ‖p-values were calculated by Mann-Whitney test.

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Table 2: MoCA Subcomponent Scores and Statistical Comparisons of Groups

	Patient Group	Control Group	*p* value†
Executive function*	4.21 (0.80)	4.86 (0.34)	**< 0.001**
Naming*	2.56 (0.53)	2.72 (0.44)	0.087
Attention*	4.75 (0.93)	5.40 (0.98)	**< 0.001**
Language*	2.51 (0.72)	2.76 (0.53)	**0.023**
Abstract thinking*	1.70 (0.46)	1.79 (0.48)	0.124
Delayed recall*	3.73 (0.98)	4.50 (0.91)	**< 0.001**
Orientation*	5.66 (0.62)	5.86 (0.39)	0.056
Total MoCA score*	25.06 (2.92)	28.08 (2.97)	**< 0.001**

MoCA: Montreal Cognitive Assessment Test. *Data were shown as mean ± standard deviation. †p-values were calculated by Mann-Whitney test. Bold p < 0.05

language score of the MoCA was significantly lower in the patient group (p= 0.023). The MoCA total score was also significantly lower in the patient group (p < 0.001). The MoCA subcomponent scores and statistical comparisons of the groups are shown in Table 2.

The DSM test values were also found to be significantly lower in the patient group (p < 0.001). Comparison of forward and reverse test results is shown in Table 3.

In the Stroop test, the time value from the 5th component was found to be 28.20 ± 8.860 sec for patient group and 24.08 ± 9.09 sec for the control group which is significantly higher in patients with constipation compared to healthy controls (p = 0.024). However, there was no significant difference between the two groups in terms of the other time values and error and correction components of the Stroop test (p > 0.05).

The correlation analyses of the patient group revealed that age did not have a significant correlation with forward, reverse span and total digit span scores, all MoCA subcomponent scores, and total MoCA score (p > 0.05). However, there was a positive correlation between education level and total MoCA score and total digit span scores ((r= 0.352, p = 0.006); (r = 0.476, p < 0.001), respectively). There was a negative correlation between The BDI score and MoCA total score and total digit span score ((r =-0.705, p < 0.001); (r = -0.465, p < 0.001), respectively). Moreover, there was a negative correlation between The BAI score and MoCA total score and total digit span score (r = -0.646, p < 0.001); (r =-0.452, p < 0.001), respectively). The correlation analysis is shown in Table 4.

DISCUSSION

In this study, the BDI and BAI scores were found to be significantly higher in patients with constipation compared to healthy controls. Our results are similar to the results of other studies in the literature. Namely, in a study that evaluated 54 patients with constipation symptoms, 23.5% of patients had depressive disorder and 34.6% had anxiety (18). Although the number of patients is limited and control group is missing, the high percentage of depression and anxiety in people with constipation is remarkable. In another study, constipation was reported to have a significant effect on mental health and has shown to increase the risk

Table 3: Digit Span Memory Test Results and Statistical Comparisons

	Patient Group	Control Group	*p* value†
Forward Digit Span*	5.18 (1.55)	6.22 (1.69)	**< 0.001**
Reverse Digit Span*	4.11 (1.18)	5.50 (1.53)	**< 0.001**
Total Digit Span Score*	9.30 (2.33)	11.72 (2.96)	**< 0.001**

*Data were shown as mean ± standard deviation. †p-values were calculated by Mann-Whitney test. Bold p < 0.05

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Table 4: Correlation Analysis

	Total Digit Span Score		Total MoCA Score	
	r	*p*	r	*p*
Education Level	0.476	**<0.001**	0.352	**0.006**
Depression Score	-0.465	**<0.001**	-0.705	**<0.001**
Anxiety Score	-0.452	**<0.001**	-0.646	**<0.001**

MoCA: Montreal Cognitive Assessment Test. Bold $p < 0.05$

of developing comorbidities such as anxiety and depression (19). Moreover, Li X et al. reported that, in addition to hidden reactions such as somatization and obsessive-compulsive disorder, anxiety and depression, were more common in patients who had constipation symptoms compared to healthy controls (6). As a result, constipation, a common issue, should not be underestimated at all.

In our study, in addition to the total MoCA score, the scores for the MoCA subcomponents, such as attention, executive function, delayed recall, and language, were found to be lower in patients with constipation compared to the control group. We think that these results are important in terms of showing which subcomponents of cognitive deterioration are responsible for causing difficulties in maintaining daily life activities in people with constipation. However, contrary to our results, Dore MP et al. reported that there was no correlation between constipation and cognitive functions (20). However, the fact that this study was conducted on the elderly population, which is known to have decreased cognitive functions due to various causes, limits its applicability for other populations (21). Moreover, constipation has also been reported to be higher in the elderly population (22). We think the investigation of cognitive functions related to constipation in the elderly population may not provide objective results.

In our study, the forward, reverse and total digit span values were found to be significantly lower in patients with constipation compared to healthy controls. Short-term memory, functioning memory, and attention, are important in terms of pointing to the negative effects of constipation in memory and attention areas.

Although all time values of the Stroop test were higher in the patient group, only the 5th time value was found to be significantly higher. There was no significant difference between the two groups in terms of error and correction values. This implies that constipation has a negative effect on advanced cognitive functions, such as focused attention, selective attention, reaction inhibition, resistance to disturbance, and rate of information processing; however, this effect is less remarkable on mild cognitive functions.

This study shows that, constipation and constipation-related comorbidities have direct or indirect negative effects on cognitive functions. We determined that some psychological disorders, such as anxiety and depression, were higher in patients with constipation compared to healthy controls. Some studies in the literature have reported that cognitive functions are negatively affected by such psychological disorders. In one study, cognitive dysfunction was reported to be significantly higher in patients with depressive disorder compared to healthy controls (23). In another study, patients with depression were found to have significant decreases in psychomotor speed, attention, management functions, visual learning, and memory functions (24). The direct effect of constipation on cognitive functions is through the gut-brain axis. Many studies in the literature have shown that there are interactions between the gut-brain axis and neural components, including the autonomic nervous system, CNS and intestinal response (including intestinal barrier, luminal microbiota and intestinal immune response) (25-27). The interest in this issue has increased gradually with publication of the study by Lyte M et al., in which rats were treated with subclinical doses of Campylobacter jejuni and developed anxiety-like behaviours without any immune response (28). Subsequent studies have made significant progress in illuminating bidirectional interactions between the nervous system and the gastrointestinal tract. Interestingly, one of the recent studies suggests that

probiotics may be effective in treating mental disorders (29).

Our study showed a positive correlation between education level, total MoCA score and total digit span score. This results suggest that, cognitive functions rise as education level increases. We also found a negative correlation between The BDI and BAI scores, total MoCA score and total digit span score. This result shows that increased anxiety and depression had an adverse effect on cognitive functions.

Our study had some limitations. The scales used in the assessment did not have the ability to diagnose diseases, and the study was performed in a single centre. For this reason, we would like to emphasize the importance of future multicentre studies with larger sample sizes. Despite these limitations, our study is among very few studies that have investigated cognitive functions in patients with constipation. Therefore, this study will be an important basis for our future studies.

CONCLUSION

We found that patients with constipation had significantly higher levels of psychological disorders, such as anxiety and depression, which in turn negatively affected their cognitive functions. Therefore, constipation should not be underestimated for preventing the development of constipation-related comorbidities. Otherwise, a person's daily and professional life can be negatively affected, causing decreased quality of life.

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