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RESEARCH

Executive functions and psychiatric disorders in adults with iron deficiency anemia

Demir eksikliği anemisi olan yetişkinlerde yürütücü işlevler ve psikiyatrik bozukluklar

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Abstract

Purpose: The focus has been on the hematological complications of iron deficiency, while the nonhematological complications have been less studied. Its effects on cognitive functions were mostly investigated in children and adolescents. The purpose of this study is to compare the executive functioning of persons with iron deficiency anemia to healthy controls in order to determine whether they have any comorbid psychiatric disorders.

Materials and Methods: 42 patients with iron deficiency anemia and 44 healthy controls participated in this study. To investigate whether any psychiatric disorders existed, the individuals were given a Structured Clinical Interview for DSM-5 Clinician's Version. Executive functioning was assessed using the Stroop Test and the Number Sequence Learning Test.

Results: When compared to the control group, the IDA group took longer on average to complete parts 1–5 of the Stroop Test. There was no difference between the groups with regards to the results of number sequence learning test. Psychiatric illnesses were more common (43%) in the IDA group than they were in the control group (13.6%). The difference was significant when the groups were compared in terms of psychiatric disorders.

Conclusion: According to the study's findings, those with iron deficiency anemia have worse executive functioning scores than healthy controls and are more likely to have psychiatric disorders. An extensive assessment of the health consequences of iron deficiency anemia is extremely important.

Keywords:. Iron deficiency, anemia, executive functions, psychiatric disorders

Öz

Amaç: Demir eksikliğinin çoğunlukla hematolojik komplikasyonlarına odaklanılmış, hematolojik olmayan komplikasyonlar ise daha az araştırılmıştır. Bilişsel fonksiyonlar üzerine etkileri ise çoğunlukla çocuk ve ergen grubunda araştırılmıştır. Çalışmamızda demir eksikliği anemisi tanısı almış yetişkinlerde eşlik eden psikiyatrik bozukluk olup olmadığını ve sağlıklı kontrollere kıyasla yürütücü işlevlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Demir eksikliği anemisi tanısı konulmuş 42 hasta ve 44 sağlıklı kontrol çalışmaya dahil edildi. Katılımcılara, psikiyatrik bozukluk varlığı araştırmak için DSM-5 Klinisyen Versiyonu için Yapılandırılmış Klinik Görüşme uygulandı. Yürütücü işlevleri değerlendirmek için Stroop testi ve sayı dizisi öğrenme testi kullanıldı.

Bulgular: Demir eksikliği anemisi grubunda kontrol grubuna kıyasla Stroop test bölüm 1-5 tamamlama süreleri daha uzundu. Düzeltme ve hata sayıları özelinde değerlendirildiğinde sonuçlar benzerdi. Sayı dizisi öğrenme testi puanları arasında farklılık izlenmedi. Demir eksikliği anemisi grubunda toplam 18 katılımcıda (%43) psikiyatrik bozukluk tespit edilirken bu sayı kontrol grubunda 6 (%13.6) idi. Eşlik eden psikiyatrik hastalık yönünden değerlendirildiğinde gruplar arasında farklılık izlendi.

Sonuç: Bulgularımız demir eksikliği anemisi olan kişilerin yürütücü işlevler yönünden sağlıklı kontrollere göre daha kötü performans sergileyebileceğini ve psikiyatrik hastalık görülme sıklığının da bu grupta daha fazla olabileceğini göstermektedir. Demir eksikliği anemisinin sağlıkla ilgili sonuçlarının kapsamlı şekilde ele alınması son derece önemlidir.

Anahtar kelimeler: Demir eksikliği, anemi, yürütücü işlevler, psikiyatrik bozukluklar

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INTRODUCTION

Anemia is defined as the level of hemoglobin in the blood below the values considered normal for one's age and gender. Iron deficiency (ID) is one of the most prevalent dietary deficiencies and one of the main causes of anemia in both industrialized and developing nations[1]. ID typically has a prevalence of 20% or less[2]. Iron deficiency anemia (IDA) is common in preschoolers and women of reproductive age regardless of their location or socioeconomic background[3].

Iron is an element that plays an essential role in immunological functions, maintaining exercise capacity, energy and neurotransmitter metabolism, and regulation of cell growth[4,5]. In addition to the hematological manifestations of ID, there are also non-hematological manifestations such as fatigue, decreased physical endurance, defective structure or function of epithelial tissues, pica, restless legs syndrome (RLS), decreased cognitive performance and behavioral disorders[6,7].

Iron has an important role in cognitive functions such as learning and memory due to its duties in neurotransmitter metabolism. A decreased level of iron in the central nervous system may cause a disruption in the functioning of iron-related enzymes. This may lead to attention and memory problems due to disruptions in the synthesis, activity and catabolism of dopamine, serotonin and noradrenaline[8]. Also, studies suggest that iron deficiency is associated with decreased intelligence and learning ability and impaired neuropsychological functions[9]. However, studies examining the relationship between iron deficiency and cognitive dysfunction mostly focus on infancy and childhood, and studies on adult patients are very limited[10-12]. In a review examining the relationship between iron deficiency and cognitive functions, mental health, and fatigue in women of reproductive age, improvements in fatigue, mental health scores, and cognitive functions were observed after iron replacement in patients with iron deficiency[13]. In another study included women of reproductive age who were treated for IDA, it was found that the patients performed better in executive attention and working memory after iron replacement therapy[14]. As well, in the literature, it has been shown that individuals with IDA exhibit worse attention performance and that iron replacement improves attention and concentration[10,14-16]. According to the results of another recent study; women are more anemic than men, cognitive scores of anemic women are lower than men, and there is a positive correlation between all parameters of anemia and cognitive functions[17].

As well as its function in cognitive processes, IDA have been linked to several psychiatric illnesses, including depression, anxiety disorders, adult attention deficit and hyperactivity disorder, bipolar affective disorder, and sleep problems[18-21]. It was found that IDA greatly enhanced both the incidence and risk of psychiatric illnesses. Also, people with IDA who take iron supplements have a noticeably lower risk of developing psychiatric illnesses[22].

The effect of IDA on executive functions has been studied mostly in the pediatric age group, and studies in adults are limited. There are also few studies addressing the neuropsychological status of people with IDA in adults. Our study is one of the few studies dealing with the effect of IDA on executive functions and psychiatric disorders accompanying iron deficiency anemia in adults. In this respect, we think that our study may be a significant contribution to the literature. In our study, we tested the hypotheses that adults with IDA would perform worse in term of executive functions compared to healthy controls and that the incidence of psychiatric disorders in this group would be higher than in healthy controls.

MATERIALS AND METHODS

Participants

42 people who were diagnosed and followed up with IDA in the Hematology Department of Sivas Cumhuriyet University School of Medicine and recruited 44 volunteers without IDA who shared the same age, gender, and socioeconomic characteristics as the study group. Evaluations of the study group and volunteers were made in the hematology outpatient clinic. The control group was selected from individuals who applied to the internal medicine outpatient clinic for different reasons, who were not determined to have any anemia in the examinations and volunteered to participate in the study. The sample formula (n=Nt2pq / d2(N-1) + t2pq) calculated to be used in the study was used. Accordingly, the study area was determined as Sivas (approximately 450 000 population) and the prevalence of the patient group was calculated as 9.9% (iron deficiency anemia p=15%[3]; adults over 18 years old p=66 (TUIK 2022 census data[23])). Since 42 patients were included in the study, the power of the

study was calculated as 92% (in the light of basic parameters). From this point of view, the number of participants in the control group at least as much as the number of patients to prevent bias.

Inclusion criteria:

Be over 18 years old

Having a diagnosis of IDA

Not having any type of anemia other than iron deficiency anemia

Volunteer to participate in the study

Exclusion criteria:

Having any type of anemia other than IDA.

Having a severe psychiatric disorder (such as exacerbations of schizophrenia or other psychotic disorders, bipolar manic episodes).

Using drugs that can affect cognitive functions.

Participating in a similar study within the past six months.

Being old enough to make it difficult to comply with the neuropsychiatric tests.

Not being able to read and write.

Having mental retardation.

Written informed permission was acquired by each subject. The Declaration of Helsinki's recommendations were followed in the study's conduct. The Cumhuriyet University Ethics Committee evaluated and approved the protocol and processes (2022-01/54).

Measures

The researchers created a standard questionnaire to evaluate the sociodemographic factors (age, sex, educational level, and monthly income) and history of physical or mental disorders. The Structured Clinical Interview for DSM-5, Clinician Version (SCID-5-CV) was administered by the same psychiatrist (YY) who took part in the study to determine whether any potential psychiatric illnesses existed. The Stroop test (ST) and the number sequence learning test were used to evaluate the subjects' EFs (NSLT; Turkish variant). The data were collected over a total of six months.

SCID-5-CV

While 32 diagnostic categories comprise comprehensive diagnostic criteria, the other 17 categories simply contain researcher questions[24]. Anyone over the age of 18 who don't have severe cognitive impairment, severe psychotic symptoms, or agitation can take it. Elbir et al. carried out the Turkish adaption and reliability study[25].

ST

It assesses how quickly information is processed as well as how well a system can withstand the disruptive impacts of automated operations. It is a performance test that is given to each person separately. Both adults and children are meant to use it. Stroop created it in its original form in 1935[26]. There are five subsections to the test, each getting harder. This study utilized the Tübitak Basic Sciences Research Group version created by Kılıç et al. by fusing the ST and Victoria variants[27].

NSLT

It is a test of learning capacity that determines how many times you must repeat a particular series of numbers before you can recall them properly. The test-taker is given a list of eight digits by the practitioner, who then asks them to repeat the list out loud. From the test, one score is obtained. It is given until the subject repeats the sequence properly twice in a row or up until the conclusion of all 12 trials. Turkish adults have had the test standardised for them[28-30].

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows version 22.0 software was used for statistical analysis (IBM Corp., Armonk, NY, USA). Shapiro-Wilk normality test was applied for continuous data to select the appropriate test. Since these variables were not suitable for normal distribution, it was decided to use non-parametric tests. Data that were not suitable the normal distribution were given as medians and quartiles. The Mann-Whitney U test (for binomial) was used because the difference tests for the control and patient groups included the comparison of the two categories. Chi-square test was also used to compare categorical variables. Spearman test was used for correlation analysis. A statistically significant p value of 0.05 was used.

RESULTS

In terms of age, gender, marital status, education level, family income level, and concomitant physical diseases, the study and control groups were comparable (p > 0.05) (Table 1). When the groups' Stroop test results were compared, it was discovered that the IDA group mean completion times for sections between 1 and 5 were longer than those of the control group's (p=0.001, p0.001, p0.001, and p=0.003, respectively); however, the results for correction and error numbers were comparable (p > 0.05).

Table 2 lists the results of the Stroop test, including the completion times, the number of errors, and the number of corrections.

Table 1. Sociodemographic characteristics and clinical features of the study sample.

	IDA group(n = 42)	Control Group (n =44)	p value
Age [median (Q1 – Q3)]	36 (30-42)	31 (27-40)	0.177
Sex (n, %)			
Male	12 (28.6)	14 (31.8)	0.743
Female	30 (71.4)	30 (68.2)	
Marital status (n, %)			0.768
Married	28 (66.7)	28 (63.6)	
Single	14 (33.3)	16 (36.4)	
Educational level (n, %)			0.990
Primary education	18 (42.9)	19 (43.2)	
High school	12 (28.6)	13 (29.5)	
University	12 (28.6)	12 (27.3)	
Household Income Level (n,%)			
Minimum wage/less than minimum wage	6 (14.3)	7 (16)	
Above the minimum wage	36 (85.7)	37 (84)	0.834
Comorbid medical illness (n,%)			1.000
Yes	4 (9.5)	4 (9)	
No	38 (90.5)	40 (91)	

IDA, Iron Deficiency Anemia; Q1, Quarter 1; Q3, Quarter 3

Table 2. Results of the IDA group and control group based on the Stroop test, including completion time and number of errors and corrections in sections 1–5. Data were given as median (Q1-Q3).

	IDA group (n = 42)	Control Group (n = 44)	p value
ST Section 1			
Completion (s)	10.00 (8.75 – 13.25)	8.00 (7.00 – 9.00)	<0.001
Error	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	1.000
Correction	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	1.000
ST Section 2			
Completion (s)	10.00 (9.00 – 12.00)	9.00 (7.00 – 9.00)	<0.001
Error	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	1.000
Correction	0.00 (0.00 – 0.25)	0.00 (0.00 – 0.00)	0.052
ST Section 3			
Completion (s)	12.00 (11.00 – 15.00)	10.00 (9.00 – 11.00)	<0.001
Error	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.165
Correction	0.00 (0.00 – 1.00)	0.00 (0.00 – 1.00)	0.953
ST Section 4			
Completion	17.00 (13.00 – 22.00)	14.00 (12.00 – 15.00)	<0.001
Error	1.00 (0.00 – 1.00)	0.00 (0.00 – 0.00)	1.000
Correction	1.00 (0.00 – 1.00)	0.00 (0.00 – 2.00)	0.564
ST Section 5			
Completion	28.00 (19.50 – 37.50)	20.00 (16.00 – 25.00)	0.003
Error	0.00 (0.00 – 1.00)	0.00 (0.00 – 0.00)	0.114
Correction	4.00 (1.00 – 5.00)	2.00 (1.00 – 3.00)	0.011

CM1, Chiari malformation type 1; SD, Standard deviation; ST, Stroop test

The medians and quartiles of the scores obtained from NSLT were 3.00 (0.00 – 16.5) in the IDA group and 11.50 (0.00 – 18.00) in the control group. No significant difference was observed between the NSLT scores (p = 0.227).

In the IDA group in 18 (43%) and in the control group in 6 (13.6%) participants psychiatric disorders were detected according to SCID-5-CV; this difference was statistically significant (p=0.003). In the IDA group, 8 (19%) anxiety disorders, 6 (14.2%) depression, 2 (4.7%) obsessive compulsive disorder (OCD) and 2 (4.7%) panic disorder were diagnosed. In the control group, 3 participants (6.8%) had anxiety disorder and 3 (6.8%) had depression. The probability of a psychiatric disease in the iron deficient group (Odds ratio) was 4.75 times higher (confidence interval 1.65-13.65, p = 0.004).

The relationship between ST results and hemoglobin, MCV, serum iron, iron binding capacity, transferrin saturation, and ferritin levels were examined by using Spearman correlation analysis. It was found that there were moderate negative correlations between the ST1 completion time and hemoglobin *(r=− 0.548; p<0.001)*, MCV *(r=− 0.575; p<0.001)*, serum iron *(r=− 0.495; p<0.001)*, iron binding capacity *(r=− 0.592) ; p<0.001)*, transferrin saturation *(r=− 0.487; p<0.001)* and ferritin *(r=− 0.527; p<0.001)* levels; moderate negative correlations between the ST2 completion time and hemoglobin *(r=− 0.471; p<0.001)*, MCV *(r=− 0.474; p<0.001)*, serum iron *(r=− 0.432; p<0.001)*, iron binding capacity *(r=− 0.495) ; p<0.001)*, transferrin saturation *(r=− 0.398; p<0.001)*, and ferritin *(r=− 0.424; p<0.001)* levels; mild to moderate negative correlations between ST3 completion time and hemoglobin level *(r=− 0.336; p=0.002)*, MCV *(r=− 0.421; p<0.001),* serum iron *(r=− 0.289; p=0.007)*, iron binding capacity *(r=− 0.340); p=0.001)*, transferrin saturation *(r=− 0.337; p=0.001)*, and ferritin *(r=− 0.294; p=0.006)* levels; and mild negative correlations between the ST4 completion time and hemoglobin *(r=− 0.377; p<0.001)*, MCV *(r=− 0.341; p=0.001)*, serum iron *(r=− 0.353; p=0.001)*, iron binding capacity *(r=− 0.405) ; p<0.001)*, transferrin saturation *(r=− 0.409; p<0.001)* and ferritin *(r=− 0.349; p=0.001)* levels. In addition, mildly negative correlations were found between ST5 completion time, which has a particularly terrible effect on executive functions, and hemoglobin *(r=− 0.310; p=0.004)*, MCV *(r=− 0.248; p=0.021)*, serum iron *(r=− 0.301; p=0.005)*, iron binding capacity *(r=− 0.321); p=0.003)*, transferrin saturation *(r=− 0.305; p=0.004)*, and ferritin *(r=− 0.289; p=0.007)* levels.

DISCUSSION

In the literature there are limited number of studies investigating the cognitive impairment observed in iron deficiency and the studies mostly include infancy and childhood. In this study, we investigated the presence of comorbid psychiatric disorders, and we examined the neurocognitive impairment associated with IDA by using various neuropsychological tests.

It has been shown that ID can cause cognitive impairment in both animals and humans. The main reason underlying this impairment is thought to be mitochondrial damage[31-33]. In animal studies, it has also been shown that ID may lead to structural and functional cerebral anomalies such as impaired dopamine and energy metabolisms and myelination[34]. It is thought that impaired monoamine oxidase activity and the resulting attention and memory problems may also be consequences of IDA[8]. Iron deficiency has been associated with the low intelligence level, decreased learning, and neuropsychological impairment[9]. Although cognitive impairment is generally associated with IDA, it should be kept in mind that ID without anemia may also be a cause of cognitive impairment[35]. In this study, we used ST and NSLT in order to evaluate the executive functions. The completion times of ST parts 1 to 5 were significantly longer in the IDA group compared to the control group, while there was no difference between the groups in terms of SDLT scores.

The ST is a neuropsychological test that evaluates functions like information processing speed, adapting the target of perception according to changing demands, restraining the disruptive effects of automatic processes, and processing parallels of stimuli that are being paid attention to and those that are not[36]. In essence, it assesses a person's capacity to focus and retain their attention based on the situation and the task at hand, to set aside distracting stimuli, to stop and suppress inappropriate inputs, and to control incorrect reaction tendencies. In our study, the IDA group's completion times for ST sections 1 through 5 were noticeably longer than those for the control group. This particularly shows that the IDA patients' attention abilities are worse than the control

group. Nevertheless, to the best of our knowledge, there was no study in which this test was applied to the adult patient population. ST was practiced in a study on teenagers with iron deficiency that was published in the literature[37]. Although different assessment tools were used in the literature than we used in this study, it has been shown that iron deficiency has a negative effect on executive functions and that there is improvement in executive functions with iron replacement.[10,13-16,38]. Our study is the first to use ST in the adult patients with IDA and it provided an important guide for future studies.

NSLT is particularly linked to hippocampal and medial prefrontal cortex activities, and it is useful to distinguish healthy people from those with conditions affecting these areas[39,40]. It is used to evaluate learning capacity and short-term memory in particular. In studies conducted to assess the executive functions of patients with IDA, it is clear from the literature that NSLT has not been used. So, there is no study to compare NSLT findings. Our study's findings demonstrate that there is no difference in the NSLT outcomes between the IDA and control groups. Yet, this needs further research, because we believe that studies using NSLT can enlighten us about executive functioning in this population.

Studies show that IDA is associated with negative psychosocial outcomes and psychiatric disorders such as anxiety disorders, depression, bipolar disorder, and sleep disorders[18-20,41]. In a hospital-based case-control study, it was found that there was a relationship between IDA and depressive disorder and the severity of depressive disorder symptoms increased with the degree of IDA[19]. A web-based survey study found a relationship between IDA and depression and psychological distress[39]. In a study examining the relationship between iron deficiency and depression in inflammatory bowel disease, it was found that the rates of anxiety and depression were higher in this patient group compared to the general population and patients with iron deficiency and anemia were at higher risk of developing depression[43]. In a case-control study, the risk of psychiatric disorders including mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, and developmental disorders was found to be higher in the IDA group[18]. In a systematic review, the relationship between iron deficiency and sleep disorders was examined and a significant relationship was found between iron deficiency and restless legs syndrome, periodic leg movements during sleep, sleep impairment, general sleep disorders, and sleep disorder associated with ADHD[44].

The risk and frequency of anxiety disorders, depression, sleep problems, and psychotic disorders are linked to iron deficiency, according to another study looking at the likelihood of developing mental disorders in individuals with IDA[22]. When we reviewed the literature, we observed that the IDA group had a greater rate of psychiatric illnesses than the control group had, including anxiety disorder, depression, obsessive compulsive disorder, and panic disorder. These findings lead us to recommend that individuals with IDA should be properly monitored for any co-occurring psychiatric problems.

The study's advantages include the fact that it is one of the few to examine the neuropsychological profile in IDA in the adult patient group, that participants were assessed using a semi-structured comprehensive interview technique, that ST and NSLT were used in this patient group for the first time, and that only patients with IDA were included. Other anemia-related factors were also excluded.

Our study has some limitations. One of these limitations is that it is a cross-sectional study. Psychiatric disorders also have the potential to negatively affect cognitive functions. For this reason, it may be difficult to distinguish the presence of a co-existing psychiatric disorder, whether the deterioration in cognitive functions is due to iron deficiency or an existing psychiatric disorder. This is another limitation of our study.

In conclusion, our findings show that psychiatric disorders may be more common in individuals with IDA than in healthy controls, and individuals with IDA may perform worse in terms of EF than without IDA. Studies in the adult patient group are quite limited. Therefore, we think that studies with a larger sample would be helpful. Repeating the tests after IDA is corrected is important for evaluating the treatment response. We think that conducting studies in which the tests are repeated after iron replacement in the same patient group may yield more meaningful results. The data gathered from studies that will use more comprehensive tests to evaluate the executive functions of patients, will contribute to our understanding of the relationship between IDA and executive functions.

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