

Can cognitive impairment be observed independently of neurological symptoms in Behçet's disease?

Behçet hastalığında nörolojik semptomlardan bağımsız olarak bilişsel bozukluk mevcut olabilir mi?

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Abstract

Purpose: Behçet's disease (BD) is a chronic, multisystem inflammatory disorder that causes mortality and morbidity. Despite data indicating cognitive impairment in patients without neurological involvement, there is currently no consensus on how to screen patients. The Montreal Cognitive Assessment (MOCA) is a practical, easy-to-use screening scale that can detect mild cognitive impairment. We aimed to detect cognitive dysfunction with MOCA in BD without neurological findings.

Materials and methods: This prospective study included patients diagnosed with BD without neurological findings, and healthy individuals matched for age, gender, and education. Behçet's Disease Current Activity Form (BDCAF) was applied to determine disease activity, and MOCA was applied to all participants.

Results: The total score of the MOCA scale was significantly lower in Behçet's patients than in the control group ($p=0.001$). While no difference was found between BD and controls in terms of MOCA subtests "Orientation" and "Abstraction" ($p=0.667$, $p=0.077$, respectively), scores in other subtests were significantly lower in patients. A negative correlation was found between BDCAF scores and total MOCA scores ($r=-0.454$, $p=0.000$). A positive correlation was found between total MOCA score and years of education ($r=0.345$, $p=0.000$).

Conclusion: In BD, a decrease in cognitive functions may exist without neurological involvement. Cognitive screening of patients with BD is crucial for detecting subclinical inflammation and improving quality of life. Our results demonstrate that the MOCA is an effective tool for detecting cognitive function decline. However, further large-scale, multi-center studies are needed to establish its routine use.

Keywords: Behçet disease, cognitive impairment, montreal cognitive assessment.

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Öz

Amaç: Behçet hastalığı (BH) birçok sistemin etkilendiği mortalite ve morbiteye yol açan kronik inflamatuvar bir hastalıktır. BH'de nörolojik tutulum bulguları olmaksızın hastalarda bilişsel fonksiyonların etkilendiğine dair veriler olsa da bu hastaların taramasına yönelik bir fikir birliğine henüz ulaşılamamıştır. Montreal Bilişsel Değerlendirme (MOBİD), hafif düzeyde bilişsel fonksiyon bozuklukları tespit edebilen pratik, kolay erişilebilir bir tarama ölçeğidir. Çalışmamızda nörolojik bulguları olmayan BH'de MOBİD ile bilişsel fonksiyon bozuklukları tespit edebilmeyi amaçladık.

Gereç ve yöntem: Bu prospektif çalışmaya BH tanısı alan ve nörolojik bulgusu olmayan hastalar ile yaş, cinsiyet ve eğitim açısından eşleştirilmiş sağlıklı bireyler dahil edildi. Hastalık aktitesini belirlemek için Behçet Hastalığı Güncel Aktivite Formu (BDCAF) uygulanırken tüm katılımcılara MOBİD uygulandı.

Bulgular: MOBİD ölçeğinin toplam puanı Behçet hastalarında kontrol grubuna göre belirgin olarak düşüktü ($p=0,001$). MOBİD alt testlerinden "Yönelim" ve "Soyutlama" açısından BH ve kontroller arasında fark saptanamamışken (sırasıyla, $p=0,667$, $p=0,077$) diğer alt testlerde puan hastalarda anlamlı olarak düşüktü. BDCAF skorlarıyla toplam MOBİD puanı arasında negatif korelasyon saptandı ($r=-0,43$, $p=0,000$). Total MOBİD puanı ile eğitim yılı arasında pozitif korelasyon saptandı ($r=0,35$, $p=0,000$).

Sonuç: BH'de nörolojik tutulum olmaksızın bilişsel fonksiyonlarda azalma mümkündür. BH'de hastaların bilişsel açıdan taranması subklinik inflamasyonun tespit edilmesi ve yaşam kalitesinin iyileştirilmesi için önemlidir. Sonuçlarımız, MOBİD tarama ölçeği ile bilişsel fonksiyonlardaki azalma pratik bir şekilde saptanabileceğini göstermiş olsa da rutin kullanıma girmesi için geniş çaplı, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Behçet hastalığı, bilişsel bozukluk, montreal bilişsel değerlendirme.

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Introduction

Behçet's disease (BD) is a chronic inflammatory disease that presents with recurrent oral and genital ulcers and ocular, vascular and neurological involvement [1-3]. The prevalence of BD varies widely according to geographical location and ethnic group. The highest prevalence was reported in Türkiye with 420 cases per 100,000 people [1, 4].

Neurological involvement in BD is one of the main causes of long-term morbidity and mortality [5]. Neurological findings associated with this condition include brainstem syndrome, a syndrome resembling multiple sclerosis, movement disorders, meningoencephalitis syndrome, myelopathic syndrome, cerebral venous sinus thrombosis, and intracranial hypertension [6]. Neurocognitive functions are a set of skills localized within the brain that include attention, information processing, memory, language, visual-perceptual processing, reasoning, impulse control, planning, and organization. These functions can be affected by acquired neurological damage [7]. Cognitive impairment is common in Behçet syndrome; working memory, recall, frontal executive functions and attention are primarily affected [8]. Cognitive dysfunction is more severe in individuals with neurological involvement but is also seen in patients without abnormal imaging findings and without other neurological symptoms [7].

It seems probable that impaired neurocognitive functioning in both BD and neuro-Behçet's disease (NBD) is the result of a number of different factors. It is evident that patients diagnosed with both BD and NBD are more prone to experiencing elevated rates of depression and anxiety disorders in comparison to individuals who are free of such ailments. It is established that these psychological disorders have an impact on neurocognition [9]. Furthermore, evidence indicates that pharmacological agents employed in therapeutic regimens, such as corticosteroids, may influence cognitive functions in BD [10].

It is also the case that neurocognitive disorders affecting memory, visuospatial awareness, attention, and frontal-executive functions can occur in patients without

neurological involvement. Such cases are sometimes referred to as "subclinical NBD" [10]. It is therefore imperative to enhance our comprehension of cognitive functioning in BD patients who do not exhibit overt neurological impairment, given that the majority of existing research has concentrated on individuals presenting with neurological symptoms.

There is a paucity of studies that evaluate cognitive functions in patients with BD. Furthermore, different assessment scales have been employed in these studies [10-13]. While it is challenging to identify an optimal method for evaluating cognitive functions in patients, there is a necessity for screening tests that can be readily administered by patients and are not time-consuming, even for mild cognitive disorders.

The Montreal Cognitive Assessment (MOCA) is a freely accessible, brief screening tool initially designed in 1996 to identify early cognitive impairment in dementia [14]. Özdilek et al. [15] demonstrated the validity and reliability of the Turkish version of the Montreal Cognitive Assessment Scale for screening cognitive dysfunction in patients with Parkinson's disease. The MOCA is a single-page, straightforward, and brief scale that can be administered in approximately 10 minutes. The scale comprises items that assess various cognitive domains, including attention, concentration, executive functions, memory, language, visual-spatial abilities, abstract thinking, and calculation.

The aim of this study was to detect neurocognitive impairment using the MOBID screening tool in patients with BD without significant neurological symptoms or history, and to investigate its association with depression, anxiety, prednisone use, neuroimaging, human leukocyte antigen (HLA-B51) and disease activity.

Materials and methods

Patients and controls

Patients over 18 with BD diagnosed at Pamukkale University Dermatology and Denizli State Hospital Rheumatology were included in the study. The study population comprised patients with BD who met the International Criteria for Behçet's Disease

(ICBD) and had no significant neurological findings, including aseptic meningitis, brainstem or spinal cord involvement, optic neuritis, epileptic seizures, peripheral neuropathy, demyelinating syndromes, stroke, and cerebral venous thrombosis. Additionally, individuals without chronic rheumatologic or dermatologic diseases, matched for age, gender, and education, were included. The following criteria were used to exclude patients from the study: a history of psychiatric disease, age below 18 years, vision loss, mental retardation, history of malignancy and substance abuse. Patients were subjected to testing for HLA-B51. The Non-Interventional Clinical Research Ethics Committee of Pamukkale University approved the study (date: 2024, number: E-60116787). All patients and control subjects provided informed consent by the Declaration of Helsinki before they participated in this study.

Clinical assessment and scales

The Beck Depression Inventory (BDI) and the BD Current Activity Form (TR-BDCAF) were administered to all subjects. The BDI is one of the most widely used self-report measures of depression in both research and clinical practice [16]. The BDCAF assesses all types of involvement and disease activity in BD [17]. This form is filled out by the clinician and is evaluated considering the day the patient arrives and the last 4 weeks. It is used for new attacks in the last 4 weeks rather than ongoing chronic inflammation. It evaluates clinical findings such as oral and genital ulcers, skin lesions, fatigue, headache, gastrointestinal lesions and joint pain or arthritis. Active findings seen in the last 4 weeks in all systems are scored and a score between 0 and 12 is obtained. Patients with more than four points are considered to have active disease. Montreal Cognitive Assessment scale was used to test cognitive functions in people with BD and healthy controls with similar educational levels. The lowest score is 0 and the highest is 30. The Turkish version has a threshold score of 21 [18].

Statistical analysis

The statistical calculations were done using the SPSS 26.0 program. Shapiro-Wilk test was used to evaluate the normality assumption.

The chi-square test was used to compare categories. Student t-test for parametric data and Mann-Whitney U test for non-parametric data. Categorical variables were expressed as a number and percentage. Continuous variables were expressed as a mean and standard deviation. Pearson correlation was used to test the linear correlation between two numerical variables when the parametric test assumptions were met. Spearman's correlation was used when the parametric test assumptions were not met. $p < 0.05$ was considered statistically significant.

Results

A total of 61 patients were included in the Behçet patient group, while the control group comprised 49 patients. The mean disease duration was 11.7 ± 6.6 years, with a BDCAF score of 5.1 ± 2.5 . No statistically significant difference was observed between the control and patient groups with regard to age, gender, educational status, and Beck Depression Scale scores ($p = 0.536$, $p = 0.876$, $p = 0.586$, $p = 0.734$, respectively). The total score of the MOCA scale, which is used to evaluate cognitive functions, was found to be significantly lower in patients with BD ($p = 0.001$). No significant difference was observed between the Behçet patient and control groups in terms of the MOCA subtests "Orientation" and "Abstraction" ($p = 0.667$, $p = 0.077$, respectively). However, the scores of the Behçet patients in the remaining subtests were found to be significantly lower (Table 1). When the patients were evaluated according to gender, the mean age in male patients was significantly lower than in female patients ($p = 0.001$). Although BDCAF scores were higher in males, the difference was not significant. ESR levels were significantly higher in female patients ($p = 0.036$). BDI scores were significantly higher in female patients than in male patients ($p = 0.033$). Although the total score of the MOCA scale and the scores of its subtests except for "Abstraction" were higher in male patients, there was no significant difference according to gender (Table 2). 21 patients with BD were using steroids. Patients using SCS had higher CRP, ESR and BDCAF scores than those not using SCS. The total MOCA scale score was higher in patients using SCS, but the difference was not statistically significant.

Table 1. Demographic, laboratory and clinical characteristics of Behçet's patients and the control group

	Behçet's patients (n=61)	Control group (n=49)	Test value	p value
Age (years)	42.9±9.1	44.4±9.0	z=-0.619	p=0.536
Gender (Female/Male)	44/17	36/12	cs:0.025	p=0.876
Average years of schooling	11.2±3.2	10.8±3.8	z=-0.545	p=0.586
ESR	19.3±17.4	13.3±12.9	z=-1.900	p=0.057
CRP	7.3±11.4	4.1±9.1	z=-3.355	p=0.001*
BDI	17.3±8.9	17.8±9.3	z=-0.274	p=0.734
MOCA-Visuospatial / Executive	3.0±1.5	4.1±1.1	z=-3.715	p=0.000*
MOCA-Naming	2.4±0.5	2.8±0.3	z=-4.500	p=0.000*
MOCA-Delayed recall	1.3±1.2	3.0±1.3	z=-2.271	p=0.023*
MOCA-Attention	4.0±1.5	4.8±1.3	z=-3.109	p=0.002*
MOCA-Language	2.6±0.7	2.6±0.6	z=-3.255	p=0.001*
MOCA-Abstraction	0.9±0.7	1.2±0.7	z=-1.771	p=0.077
MOCA- Orientation	5.5±0.9	5.7±0.5	z=-0.417	p=0.667
Total MoCA Score	20.6±4.1	24.5±3.3	z=-4.730	p=0.001*

*p<0.05, Categorical data were evaluated using chi-square test, ^z: Mann-Whitney's U test were used, Φcs: chi-square
 CRP: C reactive protein, ESR: erythrocyte sedimentation rate, BDI: Beck Depression Inventory, MOCA: Montreal Cognitive Assessment

Table 2. MOCA scores, demographic and laboratory characteristics of Behçet's disease patients according to gender

	Female (n=44)	Male (n=49)	Test value	p value
Age (years)	45.5±7.5	36.4±9.8	z=-3.434	p=0.001*
Average years of schooling	10.6±2.9	12.86±3.2	z=-2.228	p=0.026*
ESR	22.1±18.7	12.3±11.1	z=-2.029	p=0.036*
BDCAF	4.7±2.2	6.1±3.1	z=-1.594	p=0.111
BDI	19.3±9.4	13.9±6.0	z=-2.129	p=0.033*
MOCA-Visuospatial / Executive	2.9±1.6	3.2±1.2	z=-0.645	p=0.519
MOCA-Naming	2.4±0.5	2.6±0.4	z=-1.534	p=0.124
MOCA-Attention	3.9±1.6	4.1±1.2	z=-0.58	p=0.954
MOCA-Language	2.1±0.7	2.2±0.7	z=-0.305	p=0.761
MOCA-Abstraction	0.9±0.7	0.8±0.7	z=-0.647	p=0.518
MOCA- Orientation	5.5±0.9	5.7±0.4	z=-0.212	p=0.832
Total MOCA score	20.4±4.3	21.2±3.4	z=-0.323	p=0.747

*p<0.05, ^z: Mann-Whitney's U test was used. ESR erythrocyte sedimentation rate, BDCAF Behçet's Disease Current Activity Form
 BDI Beck Depression Inventory, MOCA Montreal Cognitive Assessment

There was no significant difference in MOCA subtest scores between patients using SCS and those not using SCS (Table 3). There was a link between BDCAF scores and ESR ($r=0.303$, $p=0.001$) and CRP ($r=0.359$, $p=0.000$) levels. BDCAF scores also correlated with duration of disease ($r=0.798$, $p=0.000$). However, BDCAF scores were negatively correlated with total MOCA score ($r=-0.454$, $p=0.000$). There was a positive link between the total MOCA score and the number of years of education ($r=0.345$,

$p=0.000$). Correlations of total MOCA score with clinical and demographic characteristics are summarized in Table 4. In 41 (67.2%) of the patients with BD, HLA-B51 was positive. HLA-B51 negative patients scored higher on the MOCA scale than HLA-B51 positive patients, but the difference was not statistically significant. There was no significant difference in MOCA subtest scores between HLA-B51 positive and negative patients (Table 5).

Table 3. Comparison of laboratory and assessment scale scores of Behçet's patients according to systemic corticosteroid use

	SCS used (n=21)	SCS non-used (n=40)	Test value	P value
Duration of disease (years)	11.1±6.7	12.1±6.6	$z=-0.282$	$p=0.545$
BDCAF	6.9±2.5	4.1±2.0	$z=-3.929$	$p=0.000^*$
ESR	25.3±19.9	16.1±15.1	$z=-2.172$	$p=0.030^*$
CRP	12.5±17.4	4.5±4.4	$z=-2.099$	$p=0.036^*$
BDI	21.0±8.7	16.1±8.6	$z=-2.716$	$p=0.007^*$
MOCA-Visuospatial /Executive	3.1±1.4	3.0±1.4	$z=-0.351$	$p=0.725$
MOCA-Naming	2.6±0.4	2.4±0.5	$z=-4.500$	$p=0.137$
MOCA-Attention	4.2±1.3	3.8±1.6	$z=-0.776$	$p=0.438$
MOCA-Language	2.3±0.4	2.1±0.7	$z=-1.007$	$p=0.314$
MOCA-Abstraction	0.8±0.6	0.9±0.7	$z=-0.842$	$p=0.400$
MOCA- Orientation	5.5±0.4	5.6±0.9	$z=-0.200$	$p=0.842$
Total MOCA score	21.4±3.4	20.2±4.3	$z=-0.899$	$p=0.318$

* $p<0.05$, ^z: Mann-Whitney's U test was used. SCS systemic corticosteroid, BDCAF Behçet's Disease Current Activity Form BDI Beck Depression Inventory, MOCA Montreal Cognitive Assessment

Table 4. Correlation of total MOCA score with clinical and demographic characteristics

	Total MOCA Score	
	Rho value	p value
Duration of disease (years)	$r=-0.450$	$p=0.000^*$
BDCAF	$r=-0.454$	$p=0.000^*$
Average years of schooling	$r=0.345$	$p=0.000^*$
BDI	$r=-0.125$	$p=0.192$
Age	$r=-0.238$	$p=0.013^*$

* $p<0.05$, BDCAF Behçet's Disease Current Activity Form, BDI Beck Depression Inventory, MOCA Montreal Cognitive Assessment

Table 5. Clinical characteristics, MOCA scores, and laboratory features of Behçet according to HLA-B51 positivity

	HLA-B51 positive (n=21)	HLA-B negative (n=40)	Test value	p value
Duration of disease (years)	11.1±6.7	12.1±6.6	z=-0.804	p=0.421
BDCAF	5.7±2.6	3.8±1.9	z=-3.339	p=0.001*
BDI	18.3±9.0	16.8±8.7	z=-0.445	p=0.656
MOCA-Visuospatial/ Executive	2.9±1.6	3.3±1.0	z=-0.441	p=0.659
MOCA-Naming	2.5±0.5	2.4±0.5	z=-0.180	p=0.986
MOCA-Delayed recall	2.4±1.1	2.6±1.2	z=-0.932	p=0.351
MOCA-Attention	4.0±1.5	3.9±1.3	z=-0.963	p=0.335
MOCA-Language	2.1±0.6	2.1±0.8	z=-0.671	p=0.502
MOCA-Abstraction	0.8±0.6	1.0±0.7	z=1.851	p=0.064
MOCA- Orientation	5.5±0.9	5.7±0.5	z=-0.399	p=0.690
Total MOCA score	20.2±4.3	21.3±3.6	z=-0.556	p=0.578

*p<0.05, z[∧]: Mann-Whitney's U test were used, BDCAF Behçet's Disease Current Activity Form, BDI Beck Depression Inventory
MOCA Montreal Cognitive Assessment

Discussion

In 27-75% of patients diagnosed with BD, subclinical neurological abnormalities were detected in neuroradiological, neurophysiological or neuropsychological examinations despite the absence of obvious neurological findings [19-22]. Concurrently, patients afflicted with BD who have not been diagnosed with NPH also exhibit elevated rates of cognitive impairment when compared to the general population [10-13]. Prior research has indicated that between 40% and 46% of individuals diagnosed with bipolar disorder who do not present with neurological symptoms exhibit deficits in memory and visuospatial abilities [10, 23]. In another study, 41% of patients diagnosed with bipolar disorder who did not present overt neurological symptoms were observed to exhibit deficits in executive functions, language abilities, and visual-constructional skills [13]. The present study revealed significant dysfunction in memory, language, attention, and visual-constructional abilities among patients compared to the control group.

Depression and anxiety are thought to affect cognitive functions, and there is some evidence to suggest that the neurocognitive impairment observed in BD may be attributable to this factor [24-26]. The current study revealed no

statistically significant differences between the patient and control groups with regard to anxiety and depression. Similarly, the study by Özen et al. [11] revealed no correlation between depression levels and cognitive dysfunctions. This indicates that cognitive dysfunctions cannot be attributed to psychological comorbidities in isolation.

It has been put forth that another factor influencing cognitive functions is corticosteroids, which are among the most commonly utilized treatments [27, 28]. Monastero et al. [10] reported that cognitive impairment in BD patients may occur independently of significant neurological involvement and is more common in patients receiving prednisone. Conversely, an alternative study indicated that prednisone administration had a beneficial impact on cognitive performance [22]. The findings of our study indicate that patients who were using corticosteroids exhibited a greater degree of disease activity. Nevertheless, no significant discrepancy was observed in MOCA scores between patients undergoing steroid therapy and those not receiving such treatment. These contradictory results suggest that steroids may have protective effects by suppressing inflammation, in addition to their adverse effects on the central nervous system.

The relationship between BDCAF scores in BD was previously investigated, with BDCAF scores being found to be significantly elevated in patients with cognitive dysfunction [10]. Similarly, our study revealed a negative correlation between the BDCAF score and the total MOBID score. This indicates that the disease may exert an influence on cognitive functions, in addition to other contributing factors.

HLA-B51 is a genetic marker that is frequently associated with BD. The presence of HLA-B51 may affect the clinical manifestations of the disease. Although there is no direct evidence that HLA-B51 is associated with cognitive impairment, its effects on BD, including chronic inflammation and psychological stress, have led to the assumption that it may indirectly affect cognitive dysfunction [8, 29]. However, Cavaco et al. [23] reported that they did not find an association between HLA-B51 and cognitive function in their study. Similarly, our study found no significant difference in cognitive function between patients with and without HLA-B51. Concurrently, Cavaco et al. [23] and colleagues reported that they were unable to identify a correlation between HLA-B51 and cognitive functions in their study. Similarly, our study found no significant difference in cognitive function between patients with and without HLA-B51. The findings of our study corroborate the data indicating that cognitive functions are affected despite the absence of overt neurological involvement in BD [10, 12]. It has been proposed that cognitive impairment is linked to both cerebral parenchymal lesions and brainstem lesions in NBD, while in neurologically silent BD, it is associated with white matter lesions in the frontal lobes [30]. Cognitive impairments in patients with BD have a markedly deleterious impact on quality of life and employment prospects. Early detection of cognitive dysfunction in patients with BD is the first step to improving outcomes. Given the inherent challenges associated with the administration of comprehensive neuropsychological tests in routine clinical practice, only patients exhibiting overt disease manifestations can be tested. This may result in an inadequate diagnosis and subsequent inadequate treatment. It is therefore evident that there is a need for the development

of simple, inexpensive, and sensitive brief cognitive screening tools for clinical use [13, 30].

The MOCA test has been successfully employed in the diagnosis of cognitive impairment in numerous connective tissue diseases, including Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus (SLE) [31-34]. In a previous study, the effectiveness of three screening tests, MOCA, Mini-Mental State Examination (MMSE), and Cognitive Symptom Inventory (CSI), was compared with the gold standard neuropsychological battery to determine the most effective screening test for cognitive impairment in patients with SLE. The MOCA test was reported to have the highest concordance with the gold standard test in terms of sensitivity (84%) and specificity (100%), and to be more effective than the MMSE (AUC=92.6%; sensitivity, 54.8%; specificity, 100%) and CSI (AUC=30.6%; sensitivity, 54.8%; specificity, 30.76%) screening tools [32]. Similarly, another study demonstrated that MOCA is a more effective screening test than MMSE in determining CD in SLE patients [33]. This study demonstrated that neurocognitive functions in patients with BD were significantly affected by the MOCA scale in comparison to the control group.

The limitations of the study are the relatively low sample size and the fact that a different screening questionnaire was not used for comparison. However, the study's key strengths lie in its comprehensive approach to the clinical characteristics of the patients, its prospective design, and the inclusion of a control group.

In conclusion, cognitive impairment may occur in patients with BD in the absence of overt neurological symptoms. In order to utilise the MOCA screening scale, which is a practical assessment tool, for the early detection of subclinical neurological involvement and cognitive impairment, further studies with larger patient groups in the BD patient group are required.

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Authors contributions: O.S.K.B. and U.B. have constructed/constructed the main idea and hypothesis of the study. O.S.K.B. and U.B. developed the theory and arranged/edited the material and method section. O.S.K.B., U.B., P.B. have evaluated the data in the Results section. Discussion section of the article was written by O.S.K.B. and U.B., O.S.K.B. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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