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Cognitive Functioning and Silent Neurological Manifestations in Behçet's Disease with Ocular Involvement

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ABSTRACT

Introduction: Various reports have revealed a cognitive dysfunction in Behçet's disease (BD). In this study, we aimed to assess the silent neurological manifestations, behavioral and neuropsychiological impairments of Behçet's disease patients with ocular involvement.

Methods: Thirty BD patients with ocular involvement in the nonactive phase of their illness were applied detailed neurological examination and magnetic resonance imagining (MRI). Neuropsychological tests were performed. Patients' neuropsychological performances were compared to those of healthy, demographically matched twenty subjects.

Results: Neurological manifestations of patients were headache (56.6%), pyramidal signs (13.3%), behavioral changes (3.3%) and sensory symptoms (3.3%). Four patients (13.3%) had white matter hyperintensities lesions on T2/FLAIR brain MRI. Fourteen patients (46%) had impaired cognitive performances on the following tasks: verbal memory (immediate memory p=0.000, maximal learning capacity p=0.009, number of repetitions p=0.000, total learning capacity p=0.001, recall p=0.033), nonverbal memory (immediate memory p=0.029, recall p=0.001), logical memory (immediate memory p=0.001, recall p=0.001), executive (frontal) functions (clock-drawing test p=0.000, Stroop test p=0.001, verbal fluency tests p=0.000). Patients' MMSE and clock drawing test scores were significantly lower than controls (p=0.03). Attention deficit was not detected. Behçet's disease patients showed higher scores on depression scales than healthy subjects but there was no statistically significant difference between anxiety scores.

Conclusion: Neuropsychological deficits, involving mainly memory and executive functioning, subcortical MRI lesions, and non-structural headache may be present in Behçet's disease patients with ocular involvement without overt neurological manifestations.

Keywords: Behçet's disease, cognitive impairment, headache, neuropsychology, uveitis

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INTRODUCTION

Behçet's disease (BD), first described by Turkish dermatologist, Dr. Hulusi Behçet, in 1937, is an idiopathic chronic relapsing multisystem vascular, inflammatory disease with presence of recurrent oral ulceration in addition to at least two other features: recurrent genital ulceration, typical eye lesions, typical skin lesions, or positive pathergy test (1, 2). Prevalence of BD varies based on geographic location and race, and it is seen more commonly along the Silk Route that extends from the Mediterranean region to Japan. Prevalence rates vary from 1 per 10,000 inhabitants to 42 per 10,000 inhabitants from Japan and Turkey, respectively (3, 4).

Ocular involvement has been reported in up to 70% of BD patients (5, 6). Recurrent anterior uveitis with hypopyon formation and, less frequently, retinal vasculitis are the main manifestations in the ocular system (7).

Neurological involvement is one of the most important manifestations of BD. Neurological manifestations are seen in 5% to 30% of BD patients leading to headache (migraine-like, non-structural), cerebral venous sinus thrombosis, central nervous system involvement, neuro-psycho-Behçet syndrome, peripheral nervous system involvement (1). Neuropsychiatric symptoms include personality change, mood change and general intellectual decline (8–10). In previous literature, there are several reports about cognitive impairment of neuroBehçet's disease. However, neuropsychiological deficits in Behçet's disease, without neurological involment, using standardized cognitive tests are limited. Studies show that neuropsychological data in patients with neuro-Behçet's disease have cognitive impairment especially in memory, attention and executive functioning (8, 9, 11).

It is suggested that there is an association between ocular and central nervous system manifestations in BD patients (12). To our knowledge, there are not studies reporting about ocular involvement and cognitive functioning in BD. In this study we aimed to determine the silent neurological manifestations, levels of anxiety and depression, and neuropsychiological deficits of BD patients with ocular involvement.

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METHODS

Subjects

Thirty consecutive BD patients with ocular involvement but without explicit neurological involvement in the nonactive phase of their illness were applied neurological examination at the Neurology Department of Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery. None of our patients had long term treatment and systemic conditions such as hypertension, diabetes, thyroid disorder or avitaminosis. The subjects' physical examination and blood test results were within normal limits. Patients with severe ocular involvement were excluded because of blindness might interfere with the neuropsychological tests. Twenty demographically matched healthy subjects, either volunteers or relatives, were used as controls. They performed a comprehensive battery of neuropsychological tests, and answered the anxiety and depression scales. Hospital's ethics committee approved the study and all subjects gave their informed consent.

Neurological Examination

Patients and controls were interviewed and undergone neurological examination about headache, motor symptoms, brainstem findings, disarthria, behavioral changes, dementia, seizure, cerebellar symptoms, sensory symptoms, movement disorders, hearing loss, and sphincter dysfunction. Patients with a history of perinatal brain injury, previous head trauma or any other disease that could have caused abnormal findings on neurological examination were excluded. Headache classification was performed in accordance with the International Classification of Headache Disorders 3rd edition (Beta version). None of the BD patients reported psychotic or mood disorder and all patients were sent for a cranial magnetic resonance imagining (MRI) with axial T1, T2, and proton weighted sequences.

Neuropsychological and Behavioral Evaluation

Subjects were evaluated by an experienced neuropsychologist who was unaware of patients' clinical diagnosis. Approximately 120 minutes were needed to perform the test battery. The validity and reliability of the Turkish versions of all tests were performed and reported previously. To evaluate the verbal and spatial memory, visuospatial skills, executive functioning and attention, following neuropsychological tests were applied on all patients and controls:

1- Edinburgh Handedness Inventory
2- Digit Span Test
3- Verbal Memory Processing Test (VMPT)
4- Wecshler Memory Scale (WMS)
5- Clock-drawing test
6- Language function tests; A modified Boston Naming Test (BNT)
7- Stroop Test
8- Verbal Fluency Test (animal, fruit-human being)
9- WMS Mental Control Test
10- MMSE (Mini Mental State Examination)
11- Wechsler Adult Intelligence Scale (WAIS) Similarities and Comprehension Subtests

After neuropsychological tests, the Hamilton Anxiety Scale (HAM-A) and Beck Depression Inventory (BDI) were applied to all subjects to evaluate levels of depression and anxiety.

Ocular Examination

Ocular manifestations of BD were noted that monocular or binocular panuveitis, and retinal vasculitis.

Statistical Analysis

Chi-square test, the t-test, Pearson's and Spearman's rank correlation were performed for comparison of selected variables between groups. Neuropsychological performance was analysed by direct comparison of the raw test scores between the two groups. Significance was assumed at $p<0.05$. All statistical analyses were performed using SPSS Statistics 18.0.

RESULTS

Demographic, Clinical, and Imaging Characteristics

Demographic data for each group are as follows: the average age in BD group and in control group was 33.9±10.49; 32.25±8.24, respectively, without any significant difference (p=0.549). The number of male subjects was 20 (63.3%) and female subjects was 10 (36.7%) in BD group and the number of male subjects was 13 (65.6%) and female subjects was 7 (35%) in control group, respectively, without any significant difference (P=0.903). Disease duration ranged from 2 to 24 years (mean 8.36±8.4). Mean education duration in BD and control groups were 11.03±3.30 and 12.46±3.33 in years, respectively, and significant difference was not observed between the two groups (p=0.825). Clinical manifestations of BD patients included oral aphtae (100%), uveitis (100%), genital ulcerations (93.3%), skin lesions (56.6%), fatigue (36.6%), arthritis or arthralgia (23.3%) and gastrointestinal involvement (23.3%). Neurological manifestations of patients were headache (56.6%, 17 patients), pyramidal signs (13.3%, 4 patients), behavioral changes (3.3%, 1 patients) and sensory symptoms (3.3%, 1 patient). Controls' neurological examination was normal, and 7 subjects (35%) suffered from headache. Number of patients with headache was higher than controls' but it was not statistically significant (p=0.13). Types of headaches of patients and controls are shown at Table 1. All patients had cranial MRI; 1 patient had venous angioma and 1 patient had meningioma without edema. Four patients with pyramidal signs had white matter hyperintensities lesions on T2/FLAIR brain MRI. Two of these patients had non-structural type of headache.

Behavioral and Neuropsychological Evaluation

Table 2 shows the mean scores of each neuropsychological test and behavioral questionnaires applied in the study. Fourteen patients (46%) showed more often impaired performances on the following tasks: verbal memory (immediate memory p=0.000, maximal learning capacity p=0.009, number of repetitions p=0.000, total learning capacity p=0.001, recall p=0.033), nonverbal memory (immediate memory p=0.029, recall p=0.001), logical memory (immediate memory p=0.001, recall p=0.001), executive (frontal) functions (clock-drawing test p=0.000, Stroop test p=0.001, verbal fluency tests p=0.000). Patients' MMSE and clock drawing test scores were significantly lower than controls (p=0.03). Handedness was examined with the Edinburgh Handedness Inventory and patients were classified as right-handed n=24 (80%), ambidexter n=2 (6.6%), and left-handed n=4 (13.3%). Controls were classified as left-handed n=2 (10%), ambidexter n=2 (10%), and right-handed n=16 (80%). Handedness was not statistically significant. Digit-Span test scores were similar between patients and controls and statistical analysis did not show any significant difference. Both BD patients with and without cognitive decline did not statistically differ in terms of age and education level. Only one of our patient reported that he had behavioral change as agitation after an attack of uveitis. Patients with BD showed higher scores on depression scales than controls (9.63±7.89 and 3.15±3.40, p=0.001) while anxiety scores (4.53±1.09 and 2.26±2.10, p=0.55) were not statistically significant.

DISCUSSION

It has been shown that there are changes in cognitive functioning in BD patients with neurological involvement (9, 13, 14). Brain abnormalities shown by neuroimagining techniques may explain this cognitive impairment. Studies of neuropsychological data in patients with BD

Table 1. Headache classification of subjects

	Patients	Control Group	P value*
Headache	17 (56.7%)	7 (35%)	0.133
Migraine	3 (10%)	3 (15%)	0.672
Tension like headache	3 (10%)	4 (20%)	0.277
Non-structural	11 (36.7%)	-	0.002

*Chi-square test is used.

Table 2. The mean scores of neuropsychological and psychiatric tests

Cognitive functions	Tests	Patients (n=30)	Control (n=20)	
		Mean ± SD	Mean ± SD	P value*
Attention	Digit Span Test Scale scores			
	- Forward digit span task	5.56±0.97	6.05±1.05	0.102
	- Backward digit span task	4.20±1.03	4.65±0.81	0.107
	- Total digit span task	9.76±1.83	10.77±1.78	0.069
	Reaction time	295	255	0.302
Verbal memory	Verbal Memory Processin			
	- Immediate memory	4.46±1.47	6.40±1.63	0.000
	- Maximal learningcapacity	13.56±1.83	14.60±0.75	0.009
	- Number of repetitions	7.73±1.79	5.45±2.30	0.000
	- Total learning capacity	105.26±19.41	122.50±14.78	0.001
	- Recall	11.50±2.22	12.75±1.51	0.033
	- Recognition	3.10±1.78	2.25±1.51	0.087
	- Total recall	14.60±1.45	15.00±0.00	0.142
Nonverbal memory	WMS Visual Memory Subtest			
	- Immediate memory	9.53±2.68	11.53±2.13	0.029
	- Recall	8.23±3.05	10.70±2.00	0.001
Logical memory	Immediate memory	10.86±4.03	14.95±3.72	0.001
	Recall	9.76±4.09	13.45±3.23	0.001
Executive (frontal) functions	Clock-drawing Test	8.90±1.53	11.60±0.94	0.000
	Stroop Test	16.07±4.53	14.05±1.98	0.069
	- Error	11.00	7	0.636
	- Spontaneous recovery	21.00	14.00	0.202
	Verbal Fluency Tests			
	- Animal	16.60±4.63	22.75±3.23	0.000
	- Fruit/human being	7.13±2.58	10.65±2.62	0.000
Beck Depression Inventory		9.63±7.89	3.15±3.40	0.001
MMSE		27.73±2.13	29.60±0.618	0.000
Edinburgh Handedness Inventory	Right	n=24 (80%)	n=16 (80%)	
	Ambidexter	n=2 (6.6%)	n=2 (10%)	
	Left	n=4 (13.3%)	n=2 (10%)	

*T test is used.

without neurological manifestations are limited (15, 16). In studies evaluating the cognitive performance of BD patients, it is shown that memory represents the most affected cognitive domain, followed by visuospatial/frontal executive functioning, and attention deficits are rarely affected than other cognitive abnormalities. Our study is a controlled study to evaluate cognition and silent neurological deficits in BD with ocular involvement using brain MRI. In our study, we found that memory and frontal functioning tests represented the most affected cognitive domains, and we did not detect attention deficits in BD patients. Memory deficits were as long-term learning, long-term recall, and immediate memory. Verbal and visual long-term memory deficits were the second major cognitive impairment domains; recognition memory deficit was not evaluated. Also our patients with BD showed higher scores on depression scales. It is well documentated that patients with depression should be more carefully evaluated for cognitive impairment.

Some of our BD patients had subcortical white matter lesions similar to neuroradiological findings as neuro-Behçet's disease patients. These results may demonstrate that subcortical contribution to cognitive dysfunction. Because of neurological manifestation of Behçet's disease is an important reason for comorbidity, we believe that it needs to be treated as early as possible either it is silent or overt manifestation.

Ocular involvement occurs in 67 to 95% of BD patients, and is usually in the late of the disease (17). Ocular clinical findings include iridocyclitis, hypopyon, mild to moderate vitreitis, retinal vasculitis and occlusion, optic disc hyperemia, and macular edema. Ocular manifestations may be associated with neurologic manifestations (12, 18). But there is not evidence about a relationship between ocular involvement and cognitive functioning in BD patients.

International consensus recommendation for diagnostic criteria of neuro-Behçet's Disease (NBD) is the presence of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment and in whom objective abnormalities are detected either on neurological examination, and/or with neuroimaging studies and cerebrospinal fluid (19). The prevalence of NBD in BD is approximately 5–13% in nonselected large series (20, 21). Shimizu reported that BD patients with elevated cerebral spinal fluid protein and/or cell count without overt neurological involvement might be potential NBD developers (22). Our patients did not have neurological complaints but after detailed neurological examination and MRI, we detected silent neurological findings.

Headache is the most common neurological symptom among patients with BD. Types of headaches among patients with BD are listed as non-structural headache of BD, headache due to central nervous system parenchymal involvement, headache due to cerebral venous sinus thrombosis, headache in association with ocular inflammation and co-exiting primary headaches (i. e., migraine; tension type headache) (1). Non-structural headache of BD is not primary neurological involvement in BD and it is not specific for BD, it is suggested that it may occur by the immune-mediated disease activity in susceptible individuals (23). The most common neurological manifestation of our BD patients with ocular involvement was headache, especially non-structural headache. Number of patients with headache was higher than controls' but it was not statistically significant. Furthermore, presence of headache was not considered as an evidence of neurological involvement in BD.

We evaluated neuropsychiological performance and silent neurological deficits in BD with ocular involvement and found 46% cognitive impairment among BD patients. A similar cognitive change was observed by others as well. In a neuropsychological study of patients with neuro-Behçet syndrome, Öktem and colleagues found that memory impairment was the major finding (8). The most severely affected memory process was delayed recall in the verbal and or visual modalities. Also attention deficit and deficits of executive functions of frontal system were other cognitive dysfunctions. They stated that neuropsychological status deteriorated insidiously, regardless of the neurological attacks, and the presence of cognitive decline was not directly related to lesions on neuroimaging at early stages of the disease.

Monastero and colleagues reported the cognitive functioning in BD patients without neurological involvement (15). They examined the relationship between cognitive impairment and clinical variables for cognitive impairment, and anxiety and depression levels. Similar to our results, they found that cognitive impairment was evident in 46.1% of BD patients, with memory representing the cognitive domain most affected, especially visuospatial long-term memory, followed by long-term learning, long-term recall, and verbal and visual short term memory. It is suggested that BD patients with an active disease or treated with steroid are at potential risk of having subclinical cognitive deficits. Dutra and colleagues evaluated cognitive function in BD patients with and without neurological manifestations and to analyze clinical variables associated with cognitive deficits (24). They found that both BD and NBD patients had impaired language and executive function, whereas visual memory was impaired only in NBD patients. They claimed that cognitive impairment occurs frequently in patients with BD independently of neurological manifestation and anxiety is a risk factor for cognitive impairment in BD. On behavioral evaluation of our patients, they showed higher scores on depression scales but anxiety scores were not statistically significant. Depression in our patients might be a risk factor for cognitive impairment. Severity of depression and depressive subtype have certain effects on neurocognitive task performance (25). It is difficult to comment on the clinical meaningfulness of relationship between cognitive impairment and depression in patients with BD. The neurocognitive declines and depression levels we assessed may be compared to those future studies of cognitive impairment in patients with BD. Siva and colleagues declared that patients with BD may develop a neurobehavioral syndrome, named "neuropsycho-Behçet syndrome" which consists of euphoria, disinhibition, psychomotor agitation or retardation, with paranoid attitudes and obsessive concerns (1). They claimed that the development of psychiatric symptoms either at the onset of neurological symptoms of Neuro-Behçet's disease, or independently and these symptoms are not associated with glucocorticosteroid or any other therapy (26). Only one of our patient had behavioral change as agitation. Our results support that BD patients with ocular involvement may be presented with psychiatric findings.

Gökçay et al. investigated the relationship between neuropsychological tests and P300 latancy values in patient groups with and without neurological involvement (14). Unlike our and other studies, they showed that the patient group without neurological manifestations had normal neuropsychological test results whereas the one with neurological symptoms had abnormal results. The attention deficit was the most common abnormality. Our patients did not have attention deficits. Memory disturbance, in both verbal and visual modalities was the second most common cognitive dysfunction in their study. They found that P300 latencies of the neurologically impaired group were significantly longer than the controls and asymptomatic group. They suggested that these techniques could be applied to all BD patients to follow-up of the disease. These apparent differences may be due to methodology of their research.

As patients often develop neurological involvement after some non-neurological manifestations of BD, which greatly favours a correct diagnosis and early treatment (27), Serdaroglu stressed "a careful neurological examination, including an extensive neuropsychological test battery, should be employed to detect this group" (28). The results of our study suggest that there may be neuropsychological deficits, involving mainly memory, and executive functioning, subcortical MRI lesions and non-structural headache in BD patients with ocular involvement overt neurological manifestations. Our data strongly suggests the use of a standardised cognitive examination along with a detailed neurological evaluation in detecting subclinical neurological involvement in BD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery..

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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