Is further examination necessary in patients with Behçet’s disease without any neurological signs or symptoms?

Halit Yaşar¹, Mehmet Güney Şenol², Semih Alay³, Yalçın Öner⁴, Ece Boylu⁵, Rıfat Erdem Toğrol⁶, Hakan Tekeli⁶, Mehmet Saraçoğlu⁶

Abstract
A mean percentage of 5% was reported for neurological involvement in researches related to Behçet’s disease. The neurological involvement may be characterized by headache, neuropsychiatric symptoms, brain stem involvement, cerebral venous thrombosis or peripheral nervous system involvement. Sometimes neurological involvement may be seen without any neurological sign or symptom. In our study, we aimed to evaluate the cognitive, psychiatric, and neurophysiological responses in Behçet’s disease without neurological sign and symptom. This study was performed on patients with Behçet’s disease without neurological signs and symptoms and healthy volunteers that would make the control group. The patients were assessed with Mini-Mental State Examination (MMSE), Hamilton rating scale for depression (HRSD), nerve conduction study (NCS), and visually evoked potential (VEP). A total of 27 male patients (age: 24.88±5.45 years) were enrolled in the study. Neurological examinations of all the patients were normal. Mean MMSE score of the patients was 29.62±0.79 (2 patients had loss of focus, 2 patients had disturbance in the copying function) and 2 patients had mild depression in HRSD. In the NCS, 2 patients had a right sensory-motor carpal tunnel syndrome (CTS), 1 patient had right sensory-motor CTS - bilateral ulnar nerve entrapment. In the VEP examination, 8 patients had prolonged P100 latency, decreased amplitude, and disturbance of wave morphology. VEP examination may be used as a conductive method to detect the subclinical neurological pathologies in Behçet’s disease. The possible silent neurological involvement should be evaluated with further neuro-screening methods.

Introduction
Behçet’s disease is a multisystemic chronic disease with an unknown etiology, firstly defined by Hulusi Behçet in 1937 with a triad of recurrent aphthous ulcers, genital ulcer, and uveitis and with a course of vascular, and neurological involvement (1). The disease affects the small and wide vessels of venous and arterial system, (2) and involves many systems such as mucocutaneous tissues, cardiovascular system, eyes, musculoskeletal system, gastrointestinal system, and central nervous system (CNS). In the studies, the CNS involvement is presented as about 5% of the cases (3-5) and more prominent in males with a ratio of 4:1 (6). This involvement shows itself with some signs such as headache, stroke, cognitive influence, and some psychiatric
signs. The CNS involvement in Behçet’s disease has a prominent place in morbidity and mortality. Despite the frequency of neurological signs and symptoms observed in the disease, sometimes the neurological involvement stays silent. In our study, we evaluated the presence of the peripheral nervous system, cognitive, psychiatric, and neurophysiological involvement in male Behçet patients without any prominent neurological sign or symptoms.

Patients and Methods
This study was performed on Behçet patients without prominent neurological sign or symptoms who applied to our neurology and internal medicine outpatient clinics between the dates of September-December 2006. 27 male Behçet patients who were diagnosed according to the International Behçet’s Disease Study Group Diagnostic Criteria (7) and 20 volunteer male healthy control subjects similar to the study group included the study. The control subjects were chosen from healthy volunteers who didn’t have any psychiatric complaints at present or in the past and without any past chronic disease. The inclusion criteria were to be between 20 and 55 years old, being at least primary school graduate, not to have any medical or physical impairment to take the tests or that would complicate the performance of the test, and not to have any additional internal or neurological disease, or any history of using alcohol or substance that would affect the mental state. Ethics approval is obtained from the local ethics committee of our hospital. Signed informed consent forms were obtained from the subjects in both groups.

The subjects of both groups were males. The age and educational status of both groups were statistically similar (Table 1).

The 50% (n=11) of the study group had Behçet’s disease in their close relatives. The neurological examination of all the patients and the control subjects were within normal range. Eight of the patients had disturbance with their sights.

The 66% (n=18) were using medication. The distribution of medication usage was as follows: Colchicine in 7 (39%) patients, colchicine, and azathioprine in 3 (16%), colchicine, azathioprine and acetylsalicylic acid in 1 (5.5%), infliximab in 1 (5.5%), azathioprine and prednisone in 1 (5.5%), colchicine and sulphasalazine in 1 (5.5%), acetylsalicylic acid and dobesilate in 1 (5.5%), colchicine and acetylsalicylic acid in 1 (5.5%), azathioprine and cyclosporine in 1 (5.5%), colchicine, acetylsalicylic acid, and indometacin in 1 (5.5%). The clinical signs in patients during the study are shown in Table 2.

After the demographic data of all the subjects were recorded, detailed neurological examination, and Mini-Mental State Examination (MMSE) for cognitive evaluation were performed to both groups.

Both groups were questioned for psychiatric signs or diseases according to DSM-IV (8) and Hamilton Rating Scale for Depression (HRSD) was performed. In HRSD, 0-7 score indicates no depression, 8-15 score indicates mild depression, 16-28 score indicates medium depression, and 29 or more scores indicate severe depression.

Nerve conduction study (NCS) was performed. Blood tests were performed to exclude other reasons of neuropathies before the NCS. The sensory responses of median, ulnar and sural nerve and motor and F responses of median, ulnar, peroneal, and tibial nerves from one extremity were evaluated by using the MEDELEC Multimedia EMG/EP Synergy (England) machine. The results were compared with the normal values of our neurophysiology lab.

| Table 1: The comparison of clinic and test scale results of the patient and the control group |
|------------------------------------------------------|-----------------------------------|-----------------------------------------------------|
| Variable                                             | Patient group                     | Control group                                      | p         |
| N                                                    | 27                                | 20                                                  |           |
| Age (year)                                           | 24.88±5.45                        | 26.10±3.25                                         | 0.075     |
| Educational status (year)                            | 10.92±4.37                        | 10.60±3.60                                         | 0.834     |
| Disease period (year) (min-max) (3 months-16 years)  | 2 years                           | 1 year                                              |           |
| HRSD abnormality                                     | 2                                 | 1                                                   | 1.0       |
| NCS abnormality                                      | 3                                 | 0                                                   | 0.251     |
| VEP abnormality                                      | 8                                 | 0                                                   | 0.014*    |

HRSD: Hamilton rating scale for depression, VEP: Visually evoked potentials, *p<0.05 was accepted as statistically significant, NCS: Nerve conduction study

| Table 2: The clinical findings of Behçet’s patients during the study |
|---------------------------------------------------------------|
| Symptoms                                               | Patient number (%) |
| Oral aphthous ulcers                                   | 15 (58)            |
| Visual impairment                                      | 8 (29)             |
| Genital ulcers                                        | 11 (42)            |
| Peripheral vascular involvement                        | 2 (8)              |
| Muscle and joint pain                                  | 4 (13)             |
| Malaise                                               | 1 (4)              |
| Headache                                              | 1 (4)              |
The visually evoked potential (VEP) evaluation was performed with the pattern shift technique. Concentric needle electrode was used for recording. The active electrode was placed on 2 cm above the union (Oz), and the reference electrode was placed frontally (Fz). The electrodes were connected to the MEDELEC Synergy EMG machine and the values that were gained after 100 averages for each eye were measured.

**Statistics**

Kolmogorov–Smirnov test was used to determine the normal distribution of the data. The results were expressed as mean ± standard deviation and percentages. The importance of intergroup differences was evaluated with Fisher’s exact Chi-square test and Student’s t-test. The p<0.05 value was assumed as statistically significant. All the evaluations were performed by using SPSS pocket (Version 13.0) software.

**Results**

The mean MMSE of the patient group was 29.62±0.79. 20 patients got total grades from the test (30/30), while 4 patients got 28, 27, 29, and 29 scores, respectively. Two patients had loss of focus, and 2 patients had a disturbance in the copying function. The mean education period of patients who had abnormalities in MMSE was 4.4 years, and was 12.9 years in patients with normal MMSE results, which was statistically significantly higher than the former group (p<0.001). The subjects in the control group had total grades from the test and their mean MMSE score was 30.0±0.0.

According to the patient’s HRSD results, while 2 patients had mild depression (8 and 9 points); in the control group only 1 patient had mild depression (9 points). The intergroup difference was not statistically significant (p=0.613).

Three patients showed abnormal findings in the NCS. These findings were mild slowing in the upper extremity sensorial conduction, right carpal tunnel syndrome (CTS) in 1 patient, and bilateral ulnar nerve entrapment neuropathy located in the cubital tunnel. In the control group, there was no abnormality in NCS. The intergroup difference was not statistically significant (p=0.180).

In the VEP examination, 8 patients (29%) had prolonged P100 latency (Table 3). The VEP examinations were normal in the control group. The VEP abnormality in the patient group was found to be significant compared to the control group (p=0.007). Table 1 summarizes the test results and the comparisons of the patient and the control group.

**Discussion**

It is claimed that the neurological, cognitive and peripheral nervous system subclinical involvement in Behçet’s disease is much earlier, and unnoticed because it courses subclinically (9). Thus, in our study, we aimed to evaluate the Behçet patients without any neurological involvement. We detected that at least VEP could be used in Behçet patients without a neurological complaint. However, it was decided that EMG, cognitive and other psychiatric examinations are not needed.

Vasculitis is the main case in Behçet’s disease and it can involve all small and large arteries and veins (2). The onset of the disease is usually the 2nd decade and male/female ratio is close to each other. CNS involvement (Neuro-Behçet Syndrome-NBS) is one of the most severe involvements of the disease and it increases the morbidity and mortality rates. CNS involvement is shown in approximately 5% of the cases (3-5), and much more prominent in males, with a ratio of 4:1 (6). This involvement may be separated into 2 categories; intra-axial, where the brain parenchyma, especially the brain stem is involved, and extra-axial, where the dural sinuses are affected (10). Some involvements may course silently. Cognitive influence may be observed without the demonstrable cranial involvement (11). Peripheral nervous system involvement is very rare.

The affected cognitive function in Behçet patients without prominent neurological involvement were shown in studies where the neurophysiological test batteries and tests that evaluate the other cognitive functions were used and it was found that anxiety and depression plays a negative role on this interaction (11-14). Cognitive interaction is a rare early period...
finding of NBS (15). In a study, it is reported that this interaction is related to the active disease and the usage of prednisone, and it especially affects the memory component (11), wherein another study, it was detected that prednisone has positive effects on cognition (12). Prednisone is used in many patients as an immunosuppressant therapy. However, since only 1 patient was chosen in our study, we didn’t have an opportunity to compare the MMSE scores of the patients who used prednisone and who didn’t. A study that uses potentials (P300) related to measuring cognitive interaction may provide more valuable data on effects of prednisone on cognition in addition to MMSE in this comparison. In some studies that uses P300 potentials, which is thought to be related to cognition, no difference was found in P300 potentials compared to the control group in Behçet’s disease (16,17). In our study, we detected mild MMSE abnormality in 4 cases, which were related to the low educational status of the patients. No significant cognitive interaction was detected in our patients.

Anxiety and depression, which are more frequently observed in Behçet’s disease without prominent neurological involvement was shown in many studies that used different scales (11-14,18,19). In our study where we detected mild depression in 2 patients, the results were not statistically significant compared to the control group.

Monasteroa et al. in their study (11), evaluated 26 patients without neurological involvement, used neuropsychological battery, anxiety, and depression scales and compared with normal control subjects. It was reported that Behçet patients were unsuccessful compared to the control group in long time verbal and nonverbal memory and visual-spatial functions, and anxiety and depression were observed more frequently. In Behçet patients, the cognitive disturbance was shown in 46%, and it was not observed in control subjects; the most prominent interaction was observed in memory. It was reported that this interaction was more prominent with long time prednisone usage.

Gökçay et al. (17) in their study evaluated 18 Behçet patients with neurological findings, 34 patients without neurological findings with neuropsychological tests (MMSE, verbal and visual memory, stroop, clock-drawing, serial hand movements, and Luria’s alternating design test) and electrophysiological tests (P300), with including 15 patients in the control group. In this study, in Behçet patients without neurological involvement, the P300 values and neuropsychological tests were not significantly different from the control group but in neurologically symptomatic patients, prolonged P300 latency and disturbance in cognitive functions (attention 40%, memory 30%) were observed.

Despite the frequency of ocular involvement, optic neuropathy is rare in Behçet’s disease. VEP is especially sensitive in showing the conduction disturbances in prechiasmatic visual pathways. It was detected that the P100 latencies of VEP in Behçet patients without neurological involvement are significantly prolonged, compared to the control group (20-22). Stigsby et al. in the same study, detected abnormality in the brainstem auditory evoked potential in Behçet patients without neurological involvement, while they didn’t detect significant prolongation in median and tibial somatosensory evoked potentials (21). We only evaluated VEP, and of the patients that could perform VEP, 29% had prolonged P100 latencies.

Peripheral nervous system involvement is rare in Behçet patients (5,23-25). Budak et al. (26) in their studies, where they evaluated the nerve conduction and the peripheral nervous system involvement in Behçet patients without neurological involvement, found significantly prolonged, persistent tibial F responses with decreased amplitudes. Atasoy et al. (26) detected polyneuropathy in NCS in 13 of 66 Behçet patients, despite no peripheral nervous system findings. The other studies similarly showed findings that would point the need to scan peripheral nervous system involvement in asymptomatic Behçet’s disease (27-32). However, there are also studies that show no peripheral nervous system involvement in Behçet’s disease (30,33). In our study, we detected non-specific findings in only 3 patients, with no significant peripheral nervous system involvement in Behçet’s disease, while further studies are needed that include a larger cohort.

The neurological involvement is observed usually after the other symptoms of the disease come out. Despite this involvement is reported to appear in the CNS, there are case reports that show peripheral nervous system involvement or myogenic interaction (34).

The limitations of our study are that only the male patients were included due to our hospital’s characteristic, and the relatively small number of patients. The usage of only MMSE to detect the neuropsychological profile might be another lack of our study.

The presence of possible psychiatric, CNS and peripheral nervous system involvement in Behçet
patients is an entity of exclusion for the clinician. To perform all the neurological examinations in every Behçet patient without any neurological sign or symptom may be a waste of time and not cost-effective. As a result, it is not necessary to perform these examinations routinely in our young male cohort, with no neuropsychiatric and peripheral nervous system involvement. Because we detected significant VEP abnormalities in our patients, we believe that VEP examination is essential and can be used as a screening tool in Behçet patients without neurological sign or symptom in evaluation of CNS.

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