Original Article

Subclinical neurological involvement in Behçet's disease

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Context: Behçet's disease (BD) is a multisystem inflammatory disorder with unknown etiology characterized by recurrent oral and genital aphthous ulcers and uveitis. Behçet's disease can affect the central nervous system. **Aims:** We aimed to investigate subclinical neurological involvement in patients who were suffering from BD and who had no neurological symptoms. **Settings and Design:** A total of 49 patients were included in the study. For the investigation of subclinical neurological involvement, the patients received imaging and/or neurophysiologic evaluations. **Materials and Methods:** The evaluation techniques were as follows: single photon emission computed tomography, 33 patients; cranial magnetic resonance imaging (MRI), 25 patients; brainstem auditory evoked potential examination, 36 patients; and electroencephalography (EEG), 30 patients. **Statistical Analysis Used:** The Mann-Whitney U test and Wilcoxon Rank-Sum W test were used. **Results:** Patients in the MRI and EEG groups showed significantly more abnormalities than did age- and gender-matched controls. **Conclusions:** Early diagnosis of neurological involvement in BD is important in reducing or preventing complications. Cranial MRI and EEG were found to be useful for detecting subclinical neurological abnormalities in patients with Behçet's disease.

Key words: Behçet's disease, brainstem auditory evoked response, electroencephalography, magnetic resonance imaging, single photon emission cranial tomography

Behçet's disease (BD) is a multisystem inflammatory disorder with unknown etiology characterized by recurrent oral and genital aphthous ulcers and uveitis. Vasculitis is the major pathological feature.[1] It was first described in 1937 by Hulusi Behçet, a Turkish dermatologist.[2] The disease can affect the skin, joints, intestines, lungs, heart and central nervous system. Neurological involvement in BD was first reported by Knapp in 1941[1] and it is one of the most serious manifestations of the disease. The reported frequency of nervous system involvement has varied from 5.3 to 38%.[3] Neurological involvement in BD has been classified into two major forms.[4] One form can be attributed to inflammatory disease in the small veins of the parenchyma in the central nervous system (CNS), with focal or multifocal involvement and this is known as intra-axial neuro-Behçet syndrome (NBS). The other form is caused by thrombosis of the cerebral venous sinus and is known as extra-axial NBS.

In this study we aimed to investigate neurological involvement in patients with BD who had no neurological symptoms. For this aim, we used neuroimaging and neurophysiologic methods (magnetic resonance imaging [MRI], single photon emission computed tomography [SPECT], brainstem auditory evoked potential testing [BAEP] and electroencephalography [EEG]).

Materials and Methods

A total of 49 patients with BD (30 women, 19 men) with a mean age of 34.6 ± 9.6 years (range 19-58) were enrolled in this prospective study between January 2000 and January 2003. Our institution's ethics committee approved the study and informed consent was obtained from all participants. The diagnosis of BD was made according to the international criteria for diagnosis of Behçet's disease.[5] Patients were excluded from the study if they currently had any neurological symptoms or signs or if they had any history of central nervous system disorders such as cerebral infarction, hemorrhage, tumors, etc. Three patients were excluded because of positive findings in their neurological examinations.

Table 1 summarizes the organ system manifestations of BD seen in our patients. The disease was found to be active in every patient at the time of the evaluation. Therapy consisted of steroids, colchicine and vitamin B preparations. Up to the time of the study, mean disease duration was 8.05±1.32 years. Methods used for the evaluation of subclinical neurological involvement were EEG, BAEP, MRI and SPECT. Findings from these were

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Table 1: Patients' clinical status

Clinical findings	Male/Female
Oral ulcers	19/30
Genital ulcers	16/29
Skin lesions	7/16
Pathergy	8/10
Eye lesions	12/17
Arthropathy	3/10

compared with those of controls.

SPECT

A total of 33 patients (19 women, 14 men) underwent SPECT. Their mean age was 35.9 ± 10.04 years (range 19 to 58 years). The control group consisted of 23 women whose data were obtained in a study of menstrual migraine. The mean age of this group was 34.2 ± 5.2 years. Single photon emission computed tomography was performed using an Elscint SPX 6 gamma camera (Ashby GD, UK). A parallel isolated collimator for general use with low energy was selected. Data were collected in a 64 x 64 matrix and between 1.5 200 m and 360-degree angles (25 seconds/degree, 6-degree intervals). The SPECT images (coronal, sagittal and axial) were processed with backprojection and by MET2 filters. The pharmaceutical agent was 99-mTc-HMPAO. This was prepared by the addition 2.2 GBq (60 mCi) of Tc-99 m to the commercial kit (Brain SPECT, Hungary) with 0.9% saline solution to make a total of 5 ml for injection. The bottle containing the preparation was shaken mechanically for 10 min and the preparation was used within one hour. It was injected via an intravenous port as 15 mCi per patient and the imaging was started at five minutes after the injection. Two nuclear medicine specialists who had no information about the patients or controls evaluated the results. Images were evaluated qualitatively in terms of heterogeneous blood flow, focal hypoperfusions or visible asymmetries in gray matter. For quantitative analysis, Geretec two-dimensional software (Europe Nv, Belgium) was used to evaluate the images digitally. Numerical values were obtained for anterior frontal, posterior frontal, temporal, medial occipital and lateral occipital areas. For comparisons in terms of left and right sides, the value of each cerebral side was divided by that of the dominant cerebellar area.

MRI

A total of 25 patients (13 women, 12 men) underwent MRI. Scans were performed with a 0.5 Tesla (T) Vectra scanner (General Electric Medical systems, Milwaukee, USA). The images were taken at the standard position immediately after gadolinium (Gd-DTPA) injection. The patients' mean age in this group was 35.8 ± 10.39 years (19 to 58 years). The control group consisted of 20 age- and gender- matched patients (11 female, 9 male) with lumbar pain who underwent additional cranial MRI for the purpose of this study. The mean age of the control group was 30.8 ± 8.7 years. The results were evaluated by a radiologist who had no information about the patients or controls.

BAEP

Brainstem auditory evoked potential examination was performed on 36 patients (13 women, 23 men). The mean age of the patients was 36.39 ± 9.79 years (range 19 to 58 years). None of these patients had a history of hearing loss. BAEP was performed with a Medelec synergy EMG instrument (Oxford Instruments Medical, Inc, UK). One electrode was positioned at Cz and referred to the right (M2) and left (M1) mandibles. Click stimulus and noise were applied to the headphones at 90dB and 40dB, respectively. The click stimulus was applied at a frequency of 10 per second. Measurements were made in both ears as follows. In each ear, a series of 2000 stimuli was presented twice, for a total of 4000 stimuli per ear. For each ear, the average of these two trials was taken. Latencies of Waves I, III, V and I-III and III-V interwave latencies were calculated. Two neurologists evaluated the results blindly. Our laboratory normal values were accepted as a reference in place of a control group. According to these values, the Wave I, III and V latencies were accepted as 1.7 ± 0.15, 3.9 ± 0.19 and 5.93 ± 0.25 respectively.

EEG

Thirty patients (18 women, 12 men) underwent EEG evaluation. Their mean age was 35.6 ± 10.9 years (range 19 to 58 years). The control group consisted of 18 healthy people (12 women, 6 men) and their mean age was 37.8 ± 8.5 years. Electroencephalography was performed with a 21-channel digital EEG machine (Nihon Kohden, Japan). Awake EEGs were obtained with electrodes placed according to the international 10-20 placement system. Focal spikes, temporal spikes, polyspikes, occipital spikes, frontal spikes, multifocal spikes, generalized spike-wave, polyspike-wave complexes, secondary bilateral synchrony, slow spike waves, 6Hz spike waves, bursts of polyspikes, photoparoxysmal response, photomyogenic response, theta and delta waves were accepted as abnormal activity.

Statistical analyses

SPSS software was used (SPSS, Chicago). The Mann-Whitney U test and Wilcoxon Rank-Sum W test were used. A *P* value of less than 0.05 was accepted as significant.

Results

A total of 49 patients with BD (30 women, 19 men) were enrolled in this prospective study. Of these 49 patients, 33 (19 women, 14 men) underwent SPECT, 25 (13 women, 12 men) underwent MRI, 36 (13 women, 23 men) underwent BAEP and 30 (18 women, 12 men) underwent EEG. Some patients thus underwent more than one type of study.

In the SPECT group, we detected abnormalities in 15 patients (45.4%) with visual evaluation of the images [Table 2]. We also evaluated the images quantitatively by dividing a given hemisphere's activation value by that of the dominant cerebellar

Table 2: Visual evaluation of single photon emission computed tomography images

Patient no.	Sex	Age	Single photon emission computed tomography
1	F	27	Hypoperfusion in left parietotemporal region
2	F	31	Hypoperfusion in right basal ganglia and left occipital region
3	F	58	Normal
4	M	24	Hypoperfusion in left frontoparietal region
5	F	52	Normal
6	M	22	Normal
7	M	46	Normal
8	F	47	Normal
9	F	21	Hypoperfusion in left temporal region
10	M	39	Hypoperfusion in left temporoparietal region
11	M	30	Hypoperfusion in right parietotemporal region
12	M	38	Normal
13	M	31	Hypoperfusion in left parietal region
15	F	43	Normal
16	M	45	Hypoperfusion in bilateral basal ganglia
17	M	37	Normal
18	F	27	Hypoperfusion in right parietal and left temporal regions
20	F	39	Hypoperfusion in right occipital region
21	M	35	Normal
22	F	35	Hypoperfusion in left temporooccipital region
23	F	29	Normal
24	F	37	Normal hypoperfusion in right parietooccipital region
25	F	19	Hypoperfusion in left temporal region
26	M	35	Normal
29	F	29	Hypoperfusion in right parietal region
32	M	35	Normal
34	F	23	Normal
39	F	36	Hypoperfusion in right basal ganglia
44	F	37	Normal
45	M	30	Normal
46	F	35	Normal
47	F	34	Normal
49	M	54	Normal

Table 3: Results of magnetic resonance imaging evaluation

Case no.	Sex	Age	Magnetic resonance imaging
1	F	27	Brainstem atrophy, high signal intensity, Gd enhancement in pons and meningeal Gd enhancement
3	F	28	High signal intensity in right forceps minor and lateral portions of thalamus
4	M	24	Normal
6	M	22	Normal
7	F	46	Normal
8	F	47	Normal
10	M	39	Brainstem atrophy
11	M	30	Normal
14	M	34	Normal
15	F	43	Normal
16	M	45	Normal
18	F	27	Normal
21	M	35	Normal
22	F	35	Normal
24	F	37	High signal intensity and Gd enhancement in forceps minor and major, periventricular white matter, bilateral centrum semiovale and brainstem atrophy
25	F	19	Meningeal Gd enhancement
26	M	35	Normal
28	M	30	Normal
31	F	34	High signal intensity and Gd enhancement in left post int capsule, corona radiata, centrum semiovale
32		54	Bilaterally meningeal Gd enhancement, high signal intensity in basal ganglia, cerebral atrophy
32			Meningeal Gd enhancemen
33	F	55	Normal
34	F	23	High signal intensity and Gd enhancement in centrum semiovale bilaterally
44	F	32	Normal
45	M	30	Normal
47	F	34	Normal
48	F	34	Normal

area. No significant differences were found between BD patients and controls on visual evaluation ($P=0.71$) or quantitative evaluation ($P=0.33$) of the SPECT images.

In the MRI group, abnormalities were detected in nine patients (36%, Table 3). The patients with BD had significantly more abnormalities on MRI than did the control group ($P=0.03$). In the control group, one patient had areas of gliosis around the lateral ventricles.

In the patients who underwent BAEP evaluation, no significant differences were found between their findings and the normal reference values of our laboratory.

EEGs were abnormal in 11/30 (36.6%) patients with BD [Table 4]. Patients in this group had significantly more abnormalities on EEG than did healthy controls ($P=0.01$). No abnormalities on EEG were seen in the control group.

Discussion

All patients met the diagnostic criteria outlined by the international study group for Behçet's disease, with a positive diagnosis being based on the presence of recurrent oral ulceration and two or more of the following: recurrent genital ulceration, cutaneous lesions, ocular lesions or a positive pathergy test.[5] Analysis of our data revealed significant abnormalities on MRI and EEG in patients with BD.

Although we found no significant differences between BD patients and controls on SPECT, perfusional brain disorders in patients with BD have been studied previously with SPECT.[6,7] Brain SPECT has also been found to provide useful clinical information about cerebral cortical abnormalities in patients with neurobehçet's disease.[8] In neurobehçet's disease brain lesions are located more commonly in the brainstem, basal ganglia and hemispheric white matter.[9] In our study we found hypoperfusion in the basal ganglia in three patients and in the parietal, frontal, temporal or occipital regions in 13 patients. The rationale for using SPECT in this study was the possibility that detectable changes in brain perfusion might reflect brain abnormalities in BD patients who have no clinical neurological symptoms.

MRI abnormalities were significantly more frequent in our patients with BD compared to the control group. In neurobehçet's

Table 4: Patients' electroencephalography findings

Case no.	Sex	Age	Electroencephalography
1	F	27	Normal
3	F	58	Epileptiform activity
4	M	24	Normal
5	F	52	Normal
6	M	22	Epileptiform activity paroxysmal activity
7	M	46	Normal
9	F	21	Slow waves in temporal region
10	M	39	Normal
11	M	30	Normal
13	M	31	Normal
14	M	34	Normal
15	F	43	Normal
16	M	45	Epileptiform activity
19	M	32	Normal
24	F	37	Normal
25	F	19	Epileptiform activity
26	M	35	Normal
27	F	32	Epileptiform activity
28	M	30	Epileptiform activity
29	F	55	Normal
30	F	45	Slow waves in parietooccipital region
31	F	34	Slow waves in temporal region
32	M	35	Normal
33	F	55	Epileptiform activity
35	F	27	Normal
40	F	46	Epileptiform activity
43	F	28	Normal
44	F	32	Normal
45	F	30	Normal
48	F	34	Normal

disease, the most common sites of MRI lesions are brainstem, internal capsule, basal ganglia or thalamus.[10] In our patients with no neurological symptoms, the anatomic distribution of MRI abnormalities was similar to this. These abnormalities included meningeal contrast enhancement, brainstem atrophy and high signal intensities in white matter, centrum semiovale, pons and basal ganglia. Some of these lesions may have been small infarcts in silent CNS areas, because patients were excluded from this study if they had a history of short-lived transient focal signs. Our findings were also consistent with those of a study which found CNS involvement in 15 of 25 patients who had simple BD.[11] Regarding brainstem atrophy, Mirsattari *et al* reported a patient with neurobehçet's disease and secondary progressive meningoencephalitis which remained clinically and radiologically restricted to the brainstem, but on autopsy chronic active meningoencephalomyelitis involving all levels of the CNS was found, being most marked in the brainstem.[12] For our study, the only available scanner had a main field strength of 0.5 T. Although we were able to find significant abnormalities in BD patients by using this weak magnet, more abnormalities might have been detected with a stronger system.

Brainstem auditory evoked potential testing, although useful in assessing the functional integrity of the lateral acoustic pathway and in detecting severe inflammatory changes, demyelinization and brainstem atrophy, has not been used much for evaluating patients with BD. In a study of 44 patients with BD who were neurologically intact, abnormalities were detected in four patients.[13] The BAEP findings in our study were abnormal in 24 of 36 patients (66.6%).

Regarding EEG changes in patients with BD, Matsumato reported 10 patients with neurobehçet's disease who had correlated EEG changes.[14] Midorikawa performed the largest EEG study in Behçet's patients and detected abnormalities in 80% of patients with neurological involvement and in 36% of patients without neurological signs.[15] In our series we detected EEG abnormalities in 36.6% of our patients.

In conclusion, our findings suggest that subclinical neurological involvement occurs in patients with BD. Patients with normal neurological examinations might nonetheless have lesions which are too small for detection or which are situated in silent areas of the CNS. However, early diagnosis of neurological involvement in BD is important in reducing or preventing complications. The possibility of subclinical neurological disease should therefore be considered at the time when BD is first diagnosed.

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Accepted on 24-06-2006

Source of Support: Nil, **Conflict of Interest:** None declared.