Research Article

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Headache frequency and its relation with disease activity in patients with Behçet's disease: a case-control study

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Abstract

Objective: The frequency of neurologic manifestations of Behçet disease (BD) is between 5% and 30%. The most common neurologic symptoms of BD are headache, which may be due to migraine, tension-type headache (TTH), uveitis or a direct consequence of neuro-Behçet disease. We aimed to evaluate the frequency of headache and the frequency of different headache types in patients with BD with or without neurologic involvement.

Methods: One hundred two patients (44 males, 58 females) who fulfilled the International Study Group for BD classification criteria were included in the study. The control group consisted of 115 healthy subjects (41 males, 74 females) who were an age and sex-matched population. The patients were interviewed to determine a history of BD and headache.

Results: There was no significant difference between the patients and controls in terms of the presence of headache. The majority of the headaches of patients with BD were migraine and TTH. In the BD group, the mean activity score was higher in the headache group than in the headache-free group. In the subgroups, the mean BD activity score was 4.6±1.9 in patients with migraine and the mean BD activity score was 3.0±1.6 in patients with TTH. There was a significant difference between the migraine and TTH group in terms of BD activity.

Conclusion: Migraine and TTH were the most common types of headache in both the patients with BD and the control group. The activity score of the disease was found to be higher in patients with Behçet's headache. In conclusion, physicians should be aware that worsening headache may be related to disease exacerbation in patients with BD.

Keywords: Behçet's disease, headache, migraine

INTRODUCTION

Behçet's disease (BD) is a chronic inflammatory disease with unknown etiopathogenesis in which infectious agents, genetics, environmental agents, and immunologic factors have all been assigned as causative factors (1). The major reasons for disability comprise ocular, vascular, and neurologic involvement (2, 3). Neurologic involvement was observed in about 5-30% of patients with BD in a large study (4).

Patients with BD may present with different neurologic problems, related either directly or indirectly to the disease. The most common neurologic symptom is headache with or without neurologic involvement (5). The type and frequency of neurologic manifestations of BD may vary with ethnicity (6). Previous studies reported a headache frequency ranging from 8 to 70% (7-9). This variability can be explained mainly in terms of the criteria used to define the type of headache.

In this study, our aim was to define the types of headache in patients with BD, with or without overt neurologic involvement, using a questionnaire based on the International Headache Society (IHS) criteria International Classification of Headache Disorders (ICHD-3) beta (10) and compared these with a control group. Additionally, we aimed to examine any potential relationship between headache type, disease duration, and disease activity.

This study has been a poster presantation presented in the 49th National Neurology Congress, 15th-21th November 2013, Antalya, Turkey.

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METHODS

Study Population

Patients with BD who fulfilled the International Study Group criteria, and healthy controls aged over 18 years were included in this prospective, case-control study. In the region (Isparta and surroundings) where the study was conducted, there are about 120 registered patients with BD. Registered patients with BD from this area who were admitted to Süleyman Demirel University (SDU) Research Hospital Dermatology and Neurology clinics and fulfilled the diagnostic criteria for BD were included in the study. We included 102 patients who accepted to take part in the study. The inclusion of 102 patients was based on a 95% security level and +/- 4 margin of error. A careful history of headache was taken by the authors and was recorded in an electronic database with the patients' consent. This database included all questions required for the criteria of migraine or other headache types. Patients with BD with migraine, episodic and chronic tension-type headache (TTH) who fulfilled the IHS criteria ICHD-3 beta for headaches, were enrolled in the study. The control group consisted of 115 individuals who were healthy relatives of patients who were admitted to hospital. The study was conducted during a 36-month period. The study was approved by the local ethics committee of SDU School of Medicine with 72867572/050/1780 number, at the date of 13th May, 2013. The purpose of the study was fully explained to the subjects and verbal informed consent was obtained from all participants.

Definition and Collection of Clinical Information

Each patient was interviewed and a careful history of headache was taken by an examining neurologist. Headache types were ascertained according to the ICHD-3 beta criteria. Patients with primary headache were selected from individuals who fulfilled the criteria according to ICHD-3 beta. Additionally, brain imaging methods such as computed tomography or magnetic resonance imaging (MRI) and necessary laboratory examinations (e.g. erythrocyte sedimentation rate, C-reactive protein, leukocyte count) were performed for patients who were considered to have secondary headaches. Neuro-Behçet's disease (NBD) was defined as a constellation of neurologic symptoms, signs, or both, presenting as particular neurologic syndromes, usually confirmed by ancillary investigations. Further studies were conducted on patients with findings such as focal neurologic deficit and papilledema suggestive of secondary headache. Patients diagnosed with secondary headache in the presence of these findings were excluded from the study. The major secondary headache groups in this study were: traumatic, temporal arteritis, sinusitis, and metabolic headaches. Sex, age, age at the onset of BD and initiation of headache, as well as characteristics of all present and past headache disorders were evaluated in the study participants. Data on headache frequency, duration, disease activity, and accompanying symptoms were also obtained from the patients with headache. Behçet's disease activity was calculated with a current activity index form defined by Bhakta et al. (11). This activity score is widely used for routine clinical follow-up and drug trials and this form has been adapted to the Turkish language. According to this activity score, BD activity is calculated from the degree of headache, oral ulcers, genital ulcers, skin lesions, gastrointestinal symptoms, eye involvement, and nervous system involvement in the last four weeks.

Detailed neurologic and physical examinations were performed on all patients. For each patient, BD activity was calculated according to the Behçet Disease Current Activity Form (12). Magnetic resonance imaging was also performed in patients with neurologic findings suggestive of involvement of the nervous system in this disease.

Statistical Analysis

Descriptive statistics were performed for all variables. All data collected were analyzed using Statistical Package for the Social Sciences for Windows Version 15 (SPSS Inc.; Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (SD), and qualitative variables are expressed as percentage or ratio. Continuous variables between the two groups were compared using the independent Student's t test according to the suitability of normal distribution. The Chi-square test was used for qualitative variables. Potential relationships between parameters were assessed using Pearson's correlation analysis. A calculated p value of <0.05 was considered statistically significant.

RESULTS

A total of 102 patients with BD who had the disease for more than 12 months, and 115 age and sex-matched healthy controls were enrolled in the study. There were no statistically significant differences between the patients and controls with regards to age and sex (Table 1).

There was no significant difference between the patients and controls in terms of the presence of headache. Among the 102 patients with BD, 42 (41.2%) had no headache, and 60 (58.8%) had primary headache disorders. Of these 60 patients, 18 (30%) had migraine-type, 38 (63.3%) had TTH, 3 (5%) had mixed-type (migraine plus TTH), and 1 (1.7%) had cluster headache (Table 2).

No headache was determined in 51 (44.3%) of the 115 controls, whereas 64 (55.7%) had headaches. Among these 64 controls, 13 (20.3%) had migraine-type, 44 (68.8%) had chronic TTH, 5 (7.8%) had mixed-type (migraine plus TTH), and 2 (3.1%) had cluster headache. The mean duration of BD was 9.5±8.9 (range, 1-40) years. Eighty-three (81.4%) patients were using colchicine. Two of the 18 patients with BD had had migraine with aura, and 16 patients had migraine without aura. Thirteen controls had migraine without aura. Among the

control cohort, the incidence of headache was significantly higher in females than in males (p=0.002). The same was seen among patients with BD; headache was more frequent in female patients with BD (65%) than in males (50%). However, this difference was not statistically significant. The duration of headache was >5 hours in 34 (55.7%) and <4 hours in 26 (41.3%) patients with BD, whereas in the controls, the duration of headache was >5 hours in 27 (44.3%) and <4 hours in 37 (58.7%). The difference between the two groups was not statistically significant. The duration of migraine-type headache was longer in patients with BD than in controls, but the difference was not statistically significant between the two groups. In the BD group, frequency of headache was ≤ 3 per month in 32 (53.3%) patients and ≥4 per month in 28 (46.7%) patients. In the controls, the headache frequency was ≤ 3 per month in 35 (54.7%) and ≥4 per month in 29 (45.3%). The frequency of headache was similar between patients with BD and controls (Table 3).

Table 1. Descriptive and clinical characteristics of patients and controls

	Patients (n=102)	Controls (n=115)	p
Sex M/F	44/58	41/74	0.26*
Age	38.99±11.7	36.31±12.98	0.11**
Duration of Behcet's disease, months, median (min-max)	96 (12-480)	-	-
Neurologic involvement, n (%)	5 (4.9%)	-	-
Colchicine use, n (%)	83 (81.4%)	-	-
Presence of headache, n (%)	60 (58.8%)	64 (55.7%)	0.64*

*Chi-square; ** Independent samples t-test
M: male; F: female; min: minimum; max: maximum

Table 2. Prevalence of headache in patients with Behçet's disease and controls

	Patients (n=102)		Controls (n=115)	
	n	(%)	n	(%)
Headache	60	58.8*	64	55.7*
Migraine without aura	16	15.8	13	20.3
Migraine with aura	2	1.9	0	
TTH	38	63.3	44	68.8
Mixed type (migraine+TTH)	3	5.0	5	7.8
Cluster headache	1	1.7	2	3.1
Non-headache	42	41.2	51	44.3

TTH: tension-type headache
*p:0.64 (Chi-square test)

Neurologic involvement was determined in 4.9% (3 males and 2 females) of the 102 patients with BD. Headache was present in 4 of 5 patients with NBD and one patient was headache free. Three of the four patients had migraine-type headache and one had TTH. Neurologic involvement was detected in these patients according to the neurologic examination, laboratory tests, and imaging methods. In two patients, cranial MRI revealed parenchymal lesions in the brainstem and basal ganglia and migraine-type headache was detected according to the ICHD-3 beta criteria. In one patient with brain stem lesions, TTH was determined and basal ganglion lesions were detected in one patient with migraine headache. Headache was not recorded in one patient with hemispheric lesions.

The mean BD activity score was 3.7±1.9 (min 0, max 7) in the BD group with headache, whereas the mean activity score in the BD group without headache was 2.8±1.8 (p=0.012). When examining the headache subgroups, the mean BD activity score was 4.6±1.9 (min 1, max 7) in patients with BD with migraine and 3.0±1.6 (min 0, max 7) in patients with BD with TTH, and this difference was statistically significant. The mean BD activity score was higher in patients with BD with migraine (37.5) than in patients with BD with TTH (24.3) (p=0.004).

We analyzed the time of onset of headache and onset of BD in the patient group. Migraine-type headache initiated after the diagnosis of BD in 68.8% of patients with BD with migraine. Among patients with BD with TTH, headache started in 57.9% of patients after the diagnosis of BD; however, the difference was not statistically significant.

Table 3. Headache characteristics of patients with Behçet's disease and in controls

	Patients (n=60)		Controls (n=64)		
	n	(%)	n	(%)	p
Headache duration (>5 hours)	34	55.7	27	44.3	>0.05
Headache duration (<4 hours)	26	41.3	37	58.7	>0.05
Headache frequency (≤ 3 per month)	32	53.3	35	54.7	>0.05
Headache frequency (≥4 per month)	28	46.7	29	45.3	>0.05
MAS in headache group, mean±SD	3.71±1.90				
MAS in headache-free group, mean±SD	2.76±1.80				0.012
MAS in migraine group, mean±SD	4.61±1.85				
MAS in TTH group, mean±SD	3.07±1.63				0.004

MAS: mean activity score; TTH: tension-type headache; SD: standard deviation

DISCUSSION

Headache has been reported as a common symptom in BD with or without neurologic involvement (4, 5, 10, 13). We used the IHS criteria in our study to classify headache disorders as primary or secondary.

We found the frequency of headache as 58.8% in a group of 102 patients with BD; most of these patients had no overt neurologic involvement. The frequency of headache was 55.7% in the controls, which was statistically similar to the BD group. This rate is similar to the prevalence rate of headache in the general Turkish population, which was reported as 64.7%, 66%, and 56% in different studies (3, 5, 14). Wechsler et al. found this frequency as 22% in 31 patients with BD (8). In a cohort of 46 subjects with BD who were referred for neurologic examination, Serdaroglu et al. described a frequency of headache of about 56%, of whom about 37% had migraine (7). In another study, the headache frequency was found as 60% with 30% identified as migraine-type headache (9). On the other hand, in a group of 27 patients with BD without overt neurologic involvement, Monastero et al. reported a headache frequency of 88.9%, which was statistically similar to the controls, as also observed in our study (15). In an another study from Turkey, Aykutlu et al. described that migraine was the most common type of primary headache diagnosed in 45 of 118 patients (46.4%). They found the frequency of TTH as 26.8% in 26 patients (16). On the other hand, in a nationwide prevalence study for headache in Turkey, Ertas et al. reported the 1-year prevalence rate of migraine and TTH, as 16.4% and 5.1%, respectively (17).

In the present study, in the analysis of headache subgroups, the frequency of migraine was about 17.6% and TTH was 37.2% in the BD group. The high prevalence of migraine without aura (16 of 18 migraineurs) was determined in the BD group. TTH was the most frequent type of headache in patients with BD without neurologic involvement and there were no statistically significant differences in the frequency of the different types of headache between the patients with BD and controls. In contrast to previous studies, TTH was more common than migraine-type headache in the BD group in our study (5, 15, 18). Borhani reported that migraine headache but not TTH was more common in patients with BD than in controls (18). Saip et al. reported that the prevalence of migraine in patients with BD was similar to that of the general Turkish population (5). Nonetheless, TTH was less frequent in patients with BD. Kidd reported that the prevalence of migraine with visual or sensory aura was higher in patients with BD compared with the normal population (13). Kisabay et al. reported that 24 of 42 patients with BD (57%) who were consulted at the clinic presented with headache (19). Approximately half of these 24 patients had TTH while the others (58%) had migraine- type headache, and most patients reported that their headaches were more severe and frequent during or before the attacks.

Disease activity in BD is difficult to define because of its fluctuating course, lack of laboratory tests reflecting overall disease activity, absence of a standardized form to report the severity of BD manifestation, and the continual development of new diagnostic criteria (12). In the current study, the mean activity score was significantly higher in patients with BD with headache than in those without headache (p=0.012). The pathophysiology of migraine in BD is still unclear. It has been suggested that small vessel diseases such as systemic lupus erythematosus, Sjogren's syndrome, scleroderma, as well as BD, all of which are characterized by multisystemic vasculitis, may cause cerebrovascular dysregulation, leading to migraine (20). Due to this association, we calculated the disease activity score in patients BD with migraine and TTH and found higher activity scores in the migraine group than in the TTH group, with a statistically significant difference (p=0.004).

We also evaluated the relationship between the occurrence of migraine and the onset of BD. Headache began after the onset of BD in 68.8% of patients with migraine in the BD group. Similarly, headache began after disease onset in 57.9% of patients with BD with TTH.

Reports on the prevalence of neurologic involvement in BD vary widely in different studies from different countries (21-25). A frequency of 5.3% and 4.8% of NBD was reported in two earlier studies from Turkey (3, 4). In the current study, this figure was 4.9% (5/102), and mean age of these patients was 38.2±8.2 years. Migraine without aura was observed in 2 patients, mixed-type headache (migraine and TTH) was observed in 1 patient, and two patients had no headache. Neurologic involvement was seen in about 5% of patients with BD in a large cohort in two distinct patterns (4). It is important to consider NBD in a neurologic patient who has recurrent oral or genital ulcers, uveitis, or other systemic features of BD. There have been previous attempts to produce diagnostic criteria of NBD, but these have not been validated and did not gain general acceptance (26). There are two main categories of central nervous system involvement; parenchymal and non-parenchymal (27). Magnetic resonance imaging is extremely useful to determine parenchymal lesions and differentiating NBD from conditions that mimic NBD. Brainstem–thalamic–basal ganglia lesions, in the proper clinical context, can strongly support the diagnosis of acute/subacute parenchymal NBD, and on occasions can raise this possibility even when the systemic features of BD are scarce (28). Also, some authors reported that silent neurologic involvement might also occur in BD. They showed that some patients with BD had abnormalities on neurologic examination and/or abnormal findings on neurophysiologic tests on neurologic evaluation performed routinely or due to symptoms of headache (29, 30). Kurtuncu et al. reported parenchymal involvement in the majority of patients with NBD. These authors also reported that cerebral venous sinus thrombosis was the second type of involvement in these pa-

tients (31). Occlusion of the cerebral veins and sinuses may lead to intracranial hypertension without any parenchymal signs (32). In our study, we observed parenchymal involvement in patients with NBD.

An important limitation of the current study is that the patient group comes from one particular region (Mediterranean region) of Turkey. Further studies of patients with BD from different regions of the country are needed. Besides this limitation, there are some strengths of the study. The high number of patients with BD examined for the presence of headache is one of the superior features of our study. Additionally, BD disease activity scores were calculated for the patients. According to our knowledge, no other study has compared BD activity scores in patients with and without headache, as well as in subgroups of headache.

The present study shows that the frequency of headaches revealed no significant difference between the BD group and the control group. Primary headaches such as migraine and TTH were the most common causes of headache in both the patients with BD and the control group. Interestingly, the mean BD activity score was higher in patients with BD with headache compared with those without headache. No neurologic involvement was observed in the majority of patients with BD with headache. In conclusion, physicians should examine disease activity in patients with BD who present with worsened headache.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Süleyman Demirel University, School of Medicine (No:72867572/050/1780, Date: 13th May, 2013).

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

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