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Original Article

Clinical manifestations of Behçet's syndrome: A single-center cohort of 777 patients

Cemal Gürbüz[1], Demet Yalçın Kehribar[2], Metin Özgen[1]

Abstract

Objective: Behçet's syndrome (BS) is a multisystem variable vessel vasculitis characterized by skin-mucosal lesions. It can also involve the eyes, blood vessels, joints, gastrointestinal system, urogenital system, and central nervous system. BS starts in the third or fourth decade and affects both genders equally. The disease is more severe in young men. Although the sensitivity of the pathergy test (PT) is decreasing today, it is still an important clue in the diagnosis of BS. We describe the characteristics of BS in our region, retrospectively. We also analyzed the effect of gender, age, family history, and skin PT positivity status on the difference of clinical involvement.

Methods A total of 777 BS patients (391 women and 386 men; 40.0 ± 11.6 years old) who applied to our Rheumatology Department between January 2010 and June 2020 were included in the study.

Results: Of the 777 patients, 391 were female (50.3%) and 386 were male (49.7%). The mean age at diagnosis was 30.3 ± 9.8 years. The proportion of patients with BS in their family was 10.2%. Of the 777 patients, 310 (39.9%) had only mucocutaneous symptoms. Other 467 patients (60.1%) had at least one of the ocular, musculoskeletal, vascular, neurologic, intestinal, or genitourinary involvement. Serious involvements such as eye, cardiovascular, and neurologic involvement were more common in male patients.

Conclusion: BS has the different clinical phenotypes according to gender, age of onset, and skin PT positivity status. Gender influences on the major organ involvements such as eye, neurologic, and vascular.

Keywords: Behçet's syndrome, cohort, family history, manifestations, pathergy

ORCID iDs of the authors:
C.G. 0000-0002-7507-0666
D.Y.K. 0000-0002-1852-7981
M.Ö. 0000-0002-6842-2918.

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[1] Department of Rheumatology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[2] Department of Internal Medicine, Ondokuz Mayıs University School of Medicine, Samsun, Turkey

Address for Correspondence: Metin Özgen; Department of Rheumatology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey

E-mail: kehribardemet@gmail.com

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Introduction

Behçet's syndrome (BS) is a multisystem variable vessel vasculitis characterized by skin-mucosal lesions. The eye, cardiovascular system, musculoskeletal system, gastrointestinal system, urogenital system, and central nervous system can also be involved.[1,2] The three main signs of BS (oral aphthous lesion, genital ulcers [GUs], and recurrent uveitis) were identified in 1937 by the Turkish dermatologist Hulusi Behçet and termed it as the triple symptom complex.[3,4]

BS shows a different geographical distribution pattern that is more common on the ancient Silk Road. Turkey, compared to up to 420 per 100,000 people, has the highest prevalence worldwide.[5] There are a lot of studies on the clinical findings of BS in different geographies, and it has been found that the demographic and clinical features of BS vary across regions.[6]

The etiology of BS is not clear, but it has been suggested that both the adaptive and innate immune systems, genetic predisposition, and environmental factors have all been implicated.[7] The prevalence in the Eastern and Mediterranean countries, multiple cases in the same family, and HLA B5 positivity reveal the genetic contribution. The disease starts mostly in the second or third decade. Although the disease equally affects both genders, young male BS patients suffer from a relatively more serious disease.[8]

Pathergy reaction is an important clinical clue of the underlying BS, as well as a marker of disease activity. According to many published studies, the sensitivity of pathergy test (PT) has recently decreased,[9] but it is still a very valuable diagnostic factor for BS. PT positivity is less common in countries where BS is not frequent. Recently, there has been a decrease in reaction intensity and positivity due to the use of disposable needles.[10] A positive PT is extremely important in the diagnosis of BS because a positive PT result means BS with a probability of 98.9%.[11] The recently revised international criteria do not include the PT as a direct

criterion but are considered additional points if positive in a suspected BS case.[12]

There are no pathognomonic clinical features or specific laboratory findings for BS. Although there are different diagnostic criteria, the most widely used criteria for BS are the criteria published by the International Study Group (ISG). According to these criteria, in addition to the oral ulcer (OU), at least two of the other findings must be present: GU, eye involvement (uveitis and retinitis), skin lesions (papulopustular lesions [PPLs], acneiform lesions, erythema nodosum [EN] like lesions, and folliculitis), and a positive PT.[13] Recently, new International Criteria for Behçet's disease have been proposed, which emphasizes oral, genital, and ocular involvement and allows the inclusion of vascular and neurologic involvement for the diagnosis of BS.[12]

As a disease with many manifestations, the aim of most research for BS has been to identify and characterize clinical symptoms. Here, we describe the characteristics of BS in our region, retrospectively. We also analyzed the effect of gender, age of onset, family history, and skin PT positivity status on the difference of clinical involvement.

Methods

A total of 777 patients (391 women and 386 men; 39.99 ± 11.58 years old) who applied to our Rheumatology Department between January 2010 and June 2020 and diagnosed according to the (ISG) criteria or new International Criteria for Behçet's disease were included in the study.[12,13] This study was approved by the local ethics committee (OMUKAEK No.: 2020/513, July 7, 2020). Basic demographic and medical information including age, sex, age of diagnosis, family history of BS, concomitant diseases, and clinical features were recorded. Skin PT was conducted on 770 of 777 patients of the study. Seven patients did not accept the PT or did not show the result at 48th hour.

Main Points

- There was no gender difference in terms of oral ulcer, arthritis, and gastrointestinal involvement in Behçet's syndrome.
- Gender influences on the major organ involvements such as eye, neurologic, and vascular.
- The age of onset in Behçet's syndrome is a prognostic marker.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 22 software (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables are expressed as mean ± standard deviation or median (minimum–maximum), and nominal variables are expressed as the number and percentage (%). Differences in mean values for each group were evaluated using the Student's t-test, and differences in median values were evaluated using the Mann–Whitney U test. The differences between categorical variables were examined by the chi-squared test or Fisher's exact test when expected cell sizes were less than 5. A value of $P < .05$ was considered statistically significant.

Results

Of the 777 patients, 391 were female (50.3%) and 386 were male (49.7%). The mean age at diagnosis was 30.31 ± 9.77. Family history was found in 10.2% of our patients. OU was the most frequent manifestation as expected and was present almost all patients (99.5%). Of the 777 patients, 310 (39.9%) had only mucocutaneous symptoms. Other 467 patients (60.1%) had at least one of the ocular, musculoskeletal, vascular, neurologic, intestinal, or genitourinary involvement. The proportion of patients with only mucocutaneous involvement was 25.1% in males and 54.5% in females ($P < .001$). Serious involvements such as eye, cardiovascular, and neurologic involvement, which increase morbidity and mortality, were more common in male patients. Clinical manifestations of patients and their distribution according to gender are given in Table 1.

When we compared clinical involvement according to the age of diagnosis of BS, it was understood that patients with eye involvement and neurologic involvement were diagnosed at an earlier age. Although patients with vascular involvement were diagnosed at an earlier age, this was not statistically significant ($P = .052$). When we compare patients with vascular involvement with patients with only mucocutaneous involvement, patients with vascular involvement were found to be younger ($P = .034$). In terms of other involvements or family history, there was no difference in terms of BS diagnosis age. In a more comprehensive manner, there was no difference in terms of the age of diagnosis of BS between those with only mucocutaneous involvement and those with mucocutaneous and additional involvement. You can see the comparison of BS findings according to BS diagnosis age in Table 2.

Skin PT was positive in 27.1% of patients. The positivity rate was significantly higher in men (30.8% for men and 23.6% for women) ($P = .03$). In patients with positive pathergy, PPL was significantly more frequent ($P = .012$), and GU was significantly less ($P < .001$). There was no significant difference in terms of other findings. Evaluation of clinical findings according to pathergy status is given in Table 3.

Family history was found in 10.2% of our patients. We examined whether the family history had an impact on clinical findings. In those with a family history, we found that intestinal involvement was significantly higher ($P = .001$). Although superior vena cava (SVC) thrombosis is also significantly higher in those with a family history ($P = .037$), the importance of family history has not been determined in general, in patients with vascular involvement or other findings. We shared the effect of family history on clinical findings in Table 4.

When the concomitant rheumatological diseases were examined in patients with BS, ankylosing spondylitis (AS) was the most common and was seen in 29 patients (Figure 1). In addition, nine patients had familial Mediterranean fever (FMF), seven patients had rheumatoid arthritis (RA), three patients had Sjogren's syndrome, two patients had antiphospholipid syndrome (APS), one patient had systemic lupus erythematosus (SLE), one patient had gout, and two patients had FMF and sacroiliitis at the same time.

Discussion

Limited information on the influence of gender, age of onset, family history, and skin PT positivity is available on the clinical manifestations of BS.

The clinical manifestations of patients with BS in our region were presented, and clinical manifestations by gender were compared. The male-to-female ratio was nearly equal (1:1.01) in the whole cohort. Few studies investigating gender-specific differences in BS clinical manifestations reported that men were at higher risk for vascular and ocular findings. There are some inconsistencies in the occurrence of neurologic involvement or EN.[14-16]

In 2003, in Turkey, in a study that included 2,313 patients, GU and EN were more common in women, while PPLs, thrombophlebitis, eye, neurologic, pulmonary, and vascular involvement were more common in men.[16] In another study involving 1,901 patients in Korea, EN was more common in women, while ocular and vascular involvement

Table 1. Clinical manifestations of Behçet's syndrome and their distribution according to gender.

		Gender		
Clinical manifestation	Patients (n = 777) (%)	Male (n = 386) (%)	Female (n = 391) (%)	*P* value
Oral ulcer	773 (99.5)	382 (99)	391 (100)	.060
Genital ulcer	634 (81.6)	292 (75.6)	342 (87.5)	<.001
Papulopustular lesions	555 (71.4)	304 (78.8)	251 (64.2)	<.001
Erithema nodosum—like lesions	343 (44.1)	152 (39.4)	191 (48.8)	.008
Pathergy reaction	209 (27.1)	117 (30.8)	92 (23.6)	.025
Arthritis	172 (22.1)	94 (24.4)	78 (19.9)	.139
Eye involvement	230 (29.6)	142 (36.8)	88 (22.5)	<.001
Gastrointestinal involvement	14 (1.8)	7 (1.8)	7 (1.8)	.981
Genitourinary involvement	7 (0.9)	7 (1.8)	–	.007
Cardiac involvement	6 (0.8)	6 (1.6)	–	.015
Neurologic involvement	73 (9.4)	52 (13.5)	21 (5.4)	<.001
Parenchymal involvement	43 (5.5)	29 (7.5)	14 (3.6)	.017
Dural sinus thrombosis	33 (4.2)	26 (6.7)	7 (1.8)	.001
Vascular involvement	176 (22.7)	136 (35.2)	40 (10.2)	<.001
Superficial thrombophlebitis	58 (7.5)	50 (10.3)	8 (2)	<.001
Deep vein thrombosis	120 (15.4)	95 (24.6)	25 (6.4)	<.001
Post-trombotic syndrome	17 (2.2)	16 (4.1)	1 (0.3)	<.001
Pulmonary artery aneurysm	11 (1.4)	9 (2.3)	2 (0.5)	.032
Extrapulmonary artery aneurysm	7 (0.9)	4 (1)	3 (0.8)	.724
Inferior vena cava thrombosis	20 (2.6)	14 (3.6)	6 (1.5)	.066
Superior vena cava thrombosis	10 (1.3)	10 (2.6)	–	.001
Hepatic vein thrombosis	6 (0.8)	3 (0.8)	3 (0.8)	1.000
Arterial aneurysm	29 (3.7)	21 (5.4)	8 (2)	.013

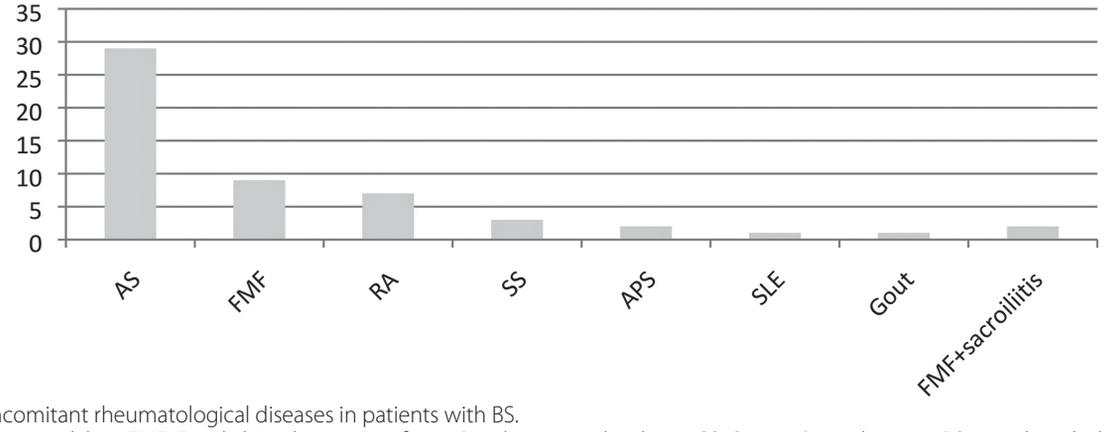

Figure 1. Concomitant rheumatological diseases in patients with BS.
AS, ankylosing spondylitis; FMF, Familial Mediterranean fever; RA, rheumatoid arthritis; SS, Sjogren's syndrome; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Table 2. Comparison of findings according to the diagnosis age of Behçet's syndrome.

	The age at diagnosis (year)		
Gender and clinical manifestations	Presence	Absence	*P* value
Female/Male	30.2 ± 9.6	30.5 ± 9.9	.699
Family history	31.5 ± 10.3	30.8 ± 9.7	.268
Additional involvement	30.0 ± 9.8	30.8 ± 9.7	.244
Skin pathergy test	30.0 ± 10.1	30.4 ± 9.7	.645
Arthritis	31.1 ± 9.9	31.0 ± 9.8	.233
Eye involvement	28.9 ± 9.4	30.9 ± 9.9	.010
Intestinal involvement	33.1 ± 8.0	30.3 ± 9.8	.287
Genitourinary involvement	26.1 ± 9.3	30.4 ± 9.8	.257
Cardiac involvement	27.0 ± 9.1	30.3 ± 30.3	.405
Neurologic involvement	27.5 ± 10.3	30.6 ± 9.7	.011
Dural sinus thrombosis	27.0 ± 10.0	30.5 ± 9.7	.030
Parenchymal involvement	28.5 ± 10.4	30.4 ± 9.7	.220
Vascular involvement	29.1 ± 10.1	30.7 ± 9.7	.052
Superficial thrombophlebitis	29.2 ± 9.3	30.4 ± 9.8	.378
Deep vein thrombosis	29.9 ± 10.5	0.4 ± 9.6	.607
Posttrombotic syndrome	27.9 ± 11.3	30.4 ± 9.7	.312
Pulmonary artery aneurysm	25.5 ± 4.7	30.4 ± 9.8	.006
Extrapulmonary artery aneurysm	36.1 ± 15.7	30.3 ± 9.7	.360
Inferior vena cava thrombosis	26.4 ± 6.9	30.4 ± 9.8	.018
Superior vena cava thrombosis	29.3 ± 7.9	30.3 ± 9.8	.741
Hepatic vein thrombosis	26.3 ± 3.1	30.4 ± 9.8	.025
Arterial thrombosis	31.5 ± 11.5	30.3 ± 9.7	.500

Table 3. Evaluation of clinical findings according to pathergy status.

		Pathergy test		
Clinical finding	Total rate (%)	Positive (%)	Negative (%)	*P* value
Oral ulcer	99.5	99.0	99.6	.30
Genital ulcer	81.6	71.3	85.4	<.001
Papulopustular lesions	71.3	78.0	68.8	.012
Erythema nodosum	44.2	47.8	42.8	.22
Eye involvement	29.2	23.9	31.2	.051
Arthritis	22.3	26.8	20.7	.80
Vascular involvement	22.3	20.6	23.0	.50
Neurologic involvement	9.4	9.6	9.3	.89
Intestinal involvement	1.8	0.5	2.3	.09
Genitourinary involvement	0.9	1.4	0.7	.35
Cardiac involvement	0.8	0.5	0.9	.56
Family history	10.1	11.0	9.8	.69

was more common in men.[14] In another study, the only finding that was more common in women was GU, while PPL, eye findings, phlebitis, and joint findings were more common in men.[17] In our cohort, GU and EN were more common in women, while PPL, pathergy reaction, eye involvement, neurologic involvement, vascular involvement, and cardiac involvement (cardiac thrombus and coronary aneurysm) were more common in men. In addition, genitourinary findings such as epididymitis and orchitis were also detected, and in some cases, these findings were the initial symptom. There was no gender difference in terms of OU, arthritis, and gastrointestinal involvement.

Age-related differences in BS attitudes have been addressed in some studies.[18–20] Yazici et al.[18] collected data on 297 BS patients and

Table 4. The effect of family history on clinical findings.

Clinical finding	Total rate (%)	Family history		*P* value
		Presence (%)	Absence (%)	
Oral ulcer	99.5	100	99.4	.50
Genital ulcer	81.6	81.0	81.7	.88
Papulopustular lesions	71.4	73.4	71.2	.79
Erythema nodosum	44.1	49.4	43.6	.34
Pathergy positivity	27.1	29.5	26.9	.69
Eye involvement	29.6	24.1	30.2	.30
Arthritis	22.1	30.4	21.2	.09
Vascular involvement	22.7	27.8	22.1	.26
Neurologic involvement	9.4	5.1	9.9	.22
Intestinal involvement	1.8	6.3	1.3	.001
Genitourinary involvement	0.9	–	1.0	.37
Cardiac involvement	0.8	–	0.9	.41

found that ocular involvement was more common in patients aged 24 or younger than patients 25 years of age and older, but did not detect age difference for other symptoms. According to another study, the average age of patients with skin lesions was lower, whereas the average age of patients with joint involvement was higher.[19] In terms of other findings, no age-related differences were detected. In another study, ocular lesions, arthritis, vascular lesions, and neurologic symptoms were observed more frequently in the elderly population, while oral ulceration, skin lesions, and genital ulceration were more common in young patients.[20] In our study, patients with eye or neurologic involvement were diagnosed at an earlier age. It was understood that patients with vascular involvement were diagnosed earlier than patients with only mucocutaneous involvement. When other findings were evaluated, there was no difference in terms of BS diagnosis age.

It was reported that PT was detected with high frequency from many countries along the Silk Road. The sensitivity of PT decreased over time and specificity increased. Positive PT result means BS with a probability of 98.4%.[9] PT can be a marker of disease activity. During the periods when major vascular involvement was active, PT positivity was higher.[21] In some studies, positive PT is associated with the presence of papulopustular lesions and GUs.[22] In a recent study from Turkey, there was no relationship between pathergy positivity rates and clinical findings such as OUs, GUs or scars, acneiform lesions, EN, and the presence of uveitis or arthritis.[21] In our study, pathergy positivity rate was 27.1%, more frequently in men. In PT positive patients, PPL was more frequent and GU was less. In terms of other findings, there was no significant difference.

The presence of family history highlights the importance of genetic contribution in the etiology of BS. Gül et al.[23] reported that the probability of BS occurrence of BS in siblings of patients with BS is 4.2%, and they predicted that familial accumulation is 11.4–52.5% in Turkey. In a comparative study conducted in 2008 to investigate the differences between juvenile-onset and adult-onset BS, the familial prevalence was observed to be 19% in juvenile BS cases and 10.3% in adult BS cases.[24] According to Akpolat et al.,[25] the frequency of familial form of BS was found to be 8.7% among 137 patients. All vascular involvements were 7.4% (2/27) in the familial group and 28.8% (36/125) in patients without familial disease. In the study performed by Ceylan Kalın et al.[26] with 840 patients, the familial prevalence was found 3.92%. In familial cases, the ages at diagnosis were found to be earlier than reported in the literature.[27] Ceylan Kalın et al.[26] found that only uveitis was less common in familial cases. As a reason for this, they predicted that uveitis can be prevented by treating familial cases with early diagnosis. While some have suggested that familial BS may be more severe than sporadic BS, the general view is that there is no significant difference. In our study, family history, previous studies conducted in a similar manner to Turkey, was found to be 10.2%. In our cohort, family history was significantly higher only in patients with intestinal involvement. In patients with vascular involvement, although the presence or absence of family history did not differ significantly, there was a significant difference in those with SVC thrombosis specifically. SVC thrombosis was more common in familial cases. Unlike some other literature studies, the presence of family history did not cause an increase in the frequency of major organ involvement except intestinal involvement or early diagnosis.

The association of BS and AS has been reported in many cases.[28,29] Nadji et al.[30] found that AS was eight to nine times more common in BS patients than the general population of Iran. Arias et al.[28] reported the incidence of AS in BS as 10%. Yazici et al.[31] reported only one case of AS among 184 BS patients in the Turkish population. There are other publications showing that there is no relationship between BS and AS.[32] AS was present in 29 (3.7%) of our 777 patients, and AS was the most common inflammatory rheumatic disease accompanying BS. Considering that the prevalence of AS is 0.25% in a study conducted in a similar geography in Turkey, it will be understood that the rate of AS in patients with BS is quite high.[33]

There is still debate whether BS and FMF occur coincidentally or there is a relation between them. The estimated prevalence of FMF in Turkey is 1/1,000.[34] In our study, we diagnosed FMF in 11 (1.4%) of 777 patients, and two of these patients also had sacroiliitis. In Turkey's eastern Black Sea region, RA is found to be 1% prevalence in the general population.[35] In our study, RA was found in 7 (0.9%) of 777 BS patients, with a similar rate to the general population.

In a study investigating the relationship of BS with Sjögren, no relationship was found

between two diseases.[36] Prevalence of Sjögren in studies ranges from 0.01% to 0.09%.[37] We diagnosed Sjögren's syndrome in three (0.04%) of our BS patients. In addition, two of our patients had APS, one patient had SLE, and one had gout.

In conclusion, our study suggested that BS has the different clinical phenotypes according to gender, age of diagnosis, and skin PT positivity status. Gender influences on the major organ involvements such as eye, neurologic, and vascular.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ondokuz Mayıs University School of Medicine (Approval Date: July 7, 2020; Approval Number: 2020/513).

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