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Original Article

Are Male Patients with Behçet's Disease Unlucky? : An Analysis of 506 Behçet Patients

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ABSTRACT

Background Behçet's Disease (BD) is characterized by oral and genital ulcers, arthritis, skin manifestations, uveitis, gastrointestinal tract, and central nervous system involvement. Although it is known to be more severe in men, there are studies in the literature with conflicting results regarding gender and the distribution of clinical findings. This study aimed to examine the relationship between clinical findings and gender in BD patients and to compare our results with the literature.

Methods 506 patients diagnosed with Behçet's disease were included in the study. Demographic data, laboratory, and clinical findings of the patients were obtained retrospectively from hospital records. The distribution of clinical findings according to gender was evaluated.

Results A total of 280 males (55.3%) and 226 females (44.7%) were included in the study. There was no significant difference between male and female patients regarding age at diagnosis (p=0.662). Genital ulcer (47.6% vs 52.4%, p=0.011), superficial thrombophlebitis (20.9% vs 79.1%, p=0.002), uveitis (33.7% vs 66.3%, p=0.02), deep vein thrombosis (22.5% vs 77.5%, p=0.001) and pulmonary artery aneurysm (11.1% vs 88.9%, p=0.046) were more common in males. There was no significant difference between the sexes in other clinical findings, HLA B5, and pathergy positivity.

Conclusion Gender impacts the clinical manifestations of BD and should be considered in patient follow-up. However, it is a heterogeneous disease, other factors may certainly affect the emergence of clinical findings.

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INTRODUCTION

Behçet's Disease (BD), first described in 1937 by Turkish dermatologist Hulusi Behçet (1889-1948), is a chronic vascular inflammatory disease of unexplained aetiology. The prevalence of Behçet's Disease is highest in Turkey, with 80-370 cases per 100,000 people. In contrast, the prevalence in Japan, China, Iran, Korea, and Saudi Arabia is 13 per 100,000.[1,2] BD is a multisystemic vasculitis characterized by recurrent oral and genital ulcers that involve eyes, skin, blood vessels, central nervous system, and gastrointestinal tract.[3] The aetiology of BD is still unclear. However, genetic factors and environmental triggers are thought to play a role. The genetic studies clarified and identified multiple robust genetic susceptibility loci for the disease.[2] The human leukocyte antigen (HLA) class I region is the most robust genetic susceptibility locus associated with Behçet's disease.[4]

BD is known to affect both sexes, with a male predominance. It has a broad clinical spectrum, and a severe course is attributed to men.[5] There are many studies in the literature investigating the clinical features and gender distribution of BD.[5-12] This study aimed to examine the relationship between clinical findings and gender in BD and to compare our results with the literature.

MATERIAL AND METHODS

According to the classification criteria of the International Study Group of BD[13] or International Criteria for Behçet's Disease (ICBD),[14] 506 patients diagnosed with Behçet's disease between 2000-2023 were included in the current study. All patients diagnosed with BD were included in the study group. Patients with no definite BD diagnosis and whose hospital records were inadequate were excluded from the study. Demographic data, laboratory, and clinical findings of the patients were obtained retrospectively from hospital records, and the distribution of clinical findings according to gender was evaluated. This study was approved by the local ethics committee (decision number: 44, date: 26.09.2023).

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) IBM software, version 23.0 statistical package program (SPSS Inc.; Chicago, IL, USA). Continuous variables are given as mean (standard deviation), and categorical variables are given as frequency and percentages. Pearson's chi-squared and Fisher's Exact chi-squared tests were used to analyse the cross-tabulations. Any $p<0.05$ value was regarded as statistically significant.

RESULTS

A total of 280 males (55.3%) and 226 females (44.7%) were included in this study. The mean age at the beginning of symptoms was 23.00±10.23 years, and the mean age at diagnosis was 29.00±9.62 years. There was no significant difference between male and female patients regarding age at diagnosis (47.50±12.22 vs 47.00±11.41, p=0.220). The clinical findings of the entire study group are summarized in Table 1.

Genital ulcer (47.6% vs 52.4%, p=0.011), superficial thrombophlebitis (20.9% vs 79.1%, p=0.002), uveitis (33.7% vs 66.3%, p=0.02), deep vein thrombosis (DVT) (22.5% vs 77.5%, p=0.001) and pulmonary artery aneurysm (PAA) (11.1% vs 88.9%, p=0.046) were more common in males. Other clinical findings showed no significant difference between the sexes (Table 1). The rate of smoking was higher in male patients than in females ($p<0.001$). Family history of oral ulcer and Behçet's disease were similar in both sexes (p=0.310 and p=0.858, respectively). There was no difference between the sexes in HLA B5 and pathergy test positivity (p=0.783 and p=0.234, respectively). In our study, there was a statistically significant relationship between gender and smoking ($p<0.05$).

DISCUSSION

Acute pancreatitis is characterized by the activation of paBD is a multi-systemic vasculitis occurring in young adults, and gender may affect clinical findings. The relationship between BD and gender varies in several studies; the male/female patient ratio was reported as 1.3, 1.53, and 1.15 in different studies from Turkey.[4,11-15] Similar to the literature data, the current study's male/female ratio was 1.23. On the other hand, there was a female predominance in studies from the Far East.[8] In the same study by Bang et al., the results of the previous studies were summarised, and there

Table 1. Comparison of sociodemographic, clinical, and laboratory features of Behçet's disease (BD) patients by gender

Clinical findings n (%)	Gender			x^2; *P value*
	Male (n: 280)	Female (n: 226)	Total (n: 506)	
Family history of oral aphthosis	44 (50.6)	43 (49.4)	87 (21.7)	1.030; 0.310
Family history of BD	28 (57.1)	21 (42.9)	49 (12.1)	0.032; 0.858
Smoking	144 (75.8)	46 (24.2)	190 (47.7)	56.230; <0.001
Oral ulcer	280 (55.1)	226 (44.9)	503 (99.4)	Fisher; 0.257
Genital ulcer	208 (52.4)	189 (47.6)	397 (78.5)	6.459; 0.011
Uveitis	124 (66.3)	63 (33.7)	187 (37.0)	14.699; <0.001
Arthritis	71 (56.8)	54 (43.2)	125 (24.7)	0.144; 0.704
Ostiofolliculitis	197 (56.9)	149 (43.1)	346 (68.4)	1.134; 0.287
Erythema nodosum	109 (55.6)	87 (44.4)	196 (38.7)	0.010; 0.921
Superficial thrombophlebitis	34 (79.1)	9 (20.9)	43 (8.5)	9.599; 0.002
Deep vein thrombosis	79 (77.5)	23 (22.5)	102 (20.4)	25.884; <0.001
Sinus vein thrombosis	20 (55.6)	16 (44.4)	36 (7.2)	0.000; 1.000
Central nervous system (parenchymal)	28 (68.3)	13 (31.7)	41 (8.2)	2.516; 0.113
Gastrointestinal system	5 (50.0)	5 (50.0)	10 (2.0)	Fisher; 0.757
Pulmonary artery aneurysm	8 (88.9)	1 (11.1)	9 (1.8)	Fisher; 0.046
Budd-Chiari syndrome	3 (1.1)	0	3 (0.6)	Fisher; 0.256
Inferior vena cava syndrome	7 (70.0)	3 (30.0)	10 (2.0)	Fisher; 0.523
Superior vena cava syndrome	5 (62.5)	3 (37.5)	8 (1.6)	Fisher; 0.737
Pulmonary artery thrombosis	11 (73.3)	4 (26.7)	15 (3.0)	1.326; 0.250
Coronary artery aneurysm	3 (100.0)	0	3 (0.6)	Fisher; 0.256
Pathergy Test	97 (55.1)	79 (44.9)	176(44.9)	1.417; 0.234
HLA B5	93 (54.7)	77 (45.3)	170(54.3)	0.076; 0.783

was a female predominance in former studies from Japan, Israel, the UK, and the USA. The reason why it is common in different geographies and different genders may be genetic and environmental factors. It is thought that age also affects the emergence of the clinical factors, but there was no significant difference between male and female patients regarding age at diagnosis. This was similar to the results of the former studies.[8]

Concerning the ISG Criteria for BD, oral aphthous lesions are the absolute condition of BD, so all patients had oral aphthous lesions. The frequency of other clinical findings differs between the sexes. Genital ulcers, superficial thrombophlebitis, uveitis, DVT, and PAA were more common in male patients than in females, and the difference was statistically significant (p values: 0.011, 0.002, <0.001, <0.001, and 0.046, respectively).

In contrast to the current literature,[8,9] genital ulcers were more common in male patients. This may result from several factors: genetic, hormonal, or environmental. Mucocutaneous lesions other than oral and genital ulcers did not differ between the sexes. The papulopustular lesions were more frequent in men, consistent with the literature, but the difference was not statistically significant. The relatively low number of patients may have prevented it from reaching statistical significance.

The incidence of DVT was significantly higher in men. Additionally, the frequency of superficial thrombophlebitis was higher in males. Other forms of vascular involvement (Budd-Chiari, vena cava superior and inferior syndrome, pulmonary thrombus, and coronary artery aneurysm) were also more common in men, but the difference was not statistically significant, probably due to the low number of patients. These findings are compatible with previous studies. Like the previous Turkish study, men had a higher ocular and vascular involvement rate.[10,15] In another study from Turkiye, vascular BD was more common in male patients.[16] The same results are reported from Korea and Germany.[8,9]

Pulmonary artery aneurysm, another vascular involvement that affects mortality, was seen in a total of 9 patients, and the difference between female (11.1%) and male (88.9%) genders was statistically significant. 10 patients (2%) with vena cava inferior syndrome (3 females, 7 males); 8 patients (1.6%) with vena cava superior syndrome (3 females, 5 males). There was one patient (0.7%) (male) with Budd-Chiari syndrome, and this relationship was not found to be statistically significant.

Neurologic involvement was more common in males, but the difference did not reach statistical

significance. This was similar to the studies from Turkey[10] but opposite to studies from Korea[8] and Japan.[17]

The pathergy test, specific for BD, was applied to 392 patients, and 44.9% were evaluated as positive. Males tended to have more positive pathergy tests than females, but the difference was insignificant. The frequency of a positive pathergy test result among genders was variable in the published studies; Tursen et al. [10] reported a similar result,whereas a study from Egypt showed an inverse relation between gender and positive pathergy test.[12]

In another study from Turkey, it was stated that the frequency of HLA-B51 antigen positivity was around 44%, similar to our study[15], which reported 56.8% of the patients were positive in the pathergy test, and in Japan, this rate was found to be 43.8%.[18] HLA B5 positivity and BD association are more evident in males.[19,20] Also, in the current study, the HLA B5 positivity was more common in males, but the difference did not reach statistical significance (54.7% vs 45.8 %, p=0.076). HLA B5 positivity may impact clinical findings, and the relatively low positivity rates compared to the literature may explain the different distribution of the clinical findings among both sexes. Also, other genetic factors, epigenetics, or non-genetic factors may play a role in the pathogenesis and clinical findings.[5]

The prognosis of BD in male patients becomes worse, especially if the patient has ocular, neurological, or vascular involvement.[21] Considering the effect of vascular involvement on mortality, it can be concluded that it is more severe in men. In the literature, there are also studies showing that genital ulcers and joint findings are at the forefront in women, and eye, skin, and vascular involvement are more common in men.[9,22] Although studies show that genetic risk is higher in men and genetic factors play a role in the different presentations of the disease, we could not show a relationship between gender and HLA B5 positivity in our patient population.[5] This suggests that genetic factors other than HLA B5 may have a role in the pathogenesis and the emergence of the clinical findings. Hormones may be another factor for the difference in clinical features between male and female patients, especially in the occurrence of mucocutaneous lesions. Hormones may play a role in the skin hemostasis and disease balance.[9] In a previous study by Yavuz et al.[23], the correlation of testosterone levels with pronounced neutrophil hyperactivity was reported, and this result was conducted with increased folliculitis, papulopustular lesions, and pathergy reactivity in males. In the current study, folliculitis, papulopustular lesions, and pathergy reactivity were more common in males, but the difference did not reach statistical significance. Environmental factors may be another reason for the differences between the sexes. The longer the time of exposure to the environment, the more it may influence clinical findings. However, the disease duration in the study group was similar in both sexes. Although the reason has not been fully elucidated, many factors cause the disease to be more severe in men.

Our study includes many patients from a single centre but has some limitations. The most important limitation of our study is its retrospective design, which may have caused data loss. Second, family history and smoking history were not recorded in all patients. Third, HLA B5 and the pathergy test were not applied to all patients. Finally, we could not investigate other genetic risk factors apart from HLA B5.

CONCLUSIONS

Gender impacts the clinical manifestations of BD and should be considered in patient follow-up. However, BD is a heterogeneous disease, other factors may certainly affect the emergence of clinical findings.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

The study received ethical approval from the Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (decision number: 44, date: 26.09.2023).

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Authors' Contribution

Study Conception: NSYB, TK; Study Design: NSYB, TK, YS; Materials: DK, MD; Data Collection: BCU, MD, RY; Analysis and interpretion: BCU,

MD, RY, YS, Literature Review: all authors; Critical Review: NSYB, TK, MD; Manuscript writing: BCU, NSYB, RY.

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