Do clinical findings of Behçet’s disease vary by gender?: A single-center experience from 329 patients

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Abstract

Objective: Behçet’s disease (BD) is a systemic vasculitis with a significantly varying clinical course following relapses and remissions, which may involve a number of organs such as the skin, joints, lungs, and blood vessels as well as systems such as the central nervous system and gastrointestinal system. Its prognosis is known to be worse in males. There are several studies in the literature on the clinical features and gender distribution of BD. The aim of the present study was to determine the clinical characteristics of BD and the presence of a relationship with gender and to investigate the correlation of our results with the current literature.

Material and Methods: We retrospectively reviewed 329 patient files. The demographic features of the patients, their symptoms and findings of BD, the results of pathergy tests, the presence of any individuals in the family with BD, and HLA-B51 antigen positivity were recorded.

Results: The most frequent findings were oral aphthous ulcers (100%), genital ulcers (84%), papulopustular lesions (69.9%), and joint involvement (57.4%). Vascular involvement and ocular involvement were significantly higher in males, whereas joint involvement and headache were more common in females (p<0.001, p=0.014, p<0.001, and p<0.001, respectively). Contrary to the literature, we found that the disease had an earlier onset in individuals with a positive familial history of an oral aphthous ulcer or BD (p=0.03 and p=0.02, respectively) and that joint involvement was more common in patients with erythema nodosum (p=0.02).

Conclusion: The clinical features of BD may vary between the genders. Variations exist in the results depending on the population size, the department where the study was conducted, the patient inclusion criteria, and the region where the patients live.

Keywords: Behçet’s disease, gender influence, vascular involvement

Introduction

Behçet’s disease (BD) is a chronic and systemic vasculitis that may affect a number of organs. It was first described by dermatologist Hulusi Behçet in 1937 as a disease presenting with recurrent aphthous stomatitis, genital ulcer, and repetitive uveitis (1). The clinical course is quite variable, changing essentially from patient to patient. A number of organs such as the skin, joints, lungs, and blood vessels as well as systems such as the central nervous system and gastrointestinal system might be involved in BD. There are differences in organ involvement and clinical course of the disease by geographical regions. Despite its worldwide existence, BD has a greater incidence, particularly in the Far East countries such as Japan, Korea, and China; in Mediterranean regions such as Turkey, Greece, and Iran; and along the ancient Silk Road, where the Middle Eastern countries are located. The prevalence in Turkey is high (2). There are several studies in the literature investigating the clinical features and gender distribution of BD and the different phenotypes of BD observed in different population groups (3-10). The aim of the present study was to determine the clinical characteristics of BD and the presence of a relationship with gender and to investigate the correlation of our results with the current literature.

Material and Methods

The files of 329 patients who were, according to the diagnostic criteria for BD of the International Study Group in 1990, diagnosed to have BD and thereupon followed-up and treated by the department of Rheumatology were successively reviewed in a retrospective manner (11). The demographic features of the patients, their symptoms and findings of BD (oral aphthous ulcer, genital ulcers, papulopustular lesions, erythema nodosum, ocular involvement, vascular involvement, headache, joint involvement, neurological involvement), the age of onset of such symptoms and findings, the results of pathergy tests, the presence of any individuals in the family with BD, and HLA-B51 antigen positivity were recorded as they could be deduced from the file data. The initial symptom starting age was taken as the disease onset age and the age at meeting the BD diagnosis measures was taken as the diagnosis age. Our study was approved by the ethics committee of Eskişehir Osmangazi University.
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Statistical analysis
We investigated whether there was any difference by gender and further whether there was any relation between the clinical findings and gender. Statistical analyses were performed using the Statistical Package for Social Science (SPSS) software, version 15.0 statistical package program (SPSS Inc.; Chicago, IL, USA). Herein, categorical variables are given in numbers or percentages, while continuous variables are expressed as the mean±standard deviation (SD). For the statistical analysis comparing the groups, the paired sample t test was used in the case of parametric data and the Mann–Whitney U test was applied in the case of non-parametric data. Any p<0.05 value was regarded as statistically significant.

Results

Gender and age
Out of 329 patients, 199 (60.4%) were males and the male to female ratio was 1.53. The mean age of disease onset was 24.3±8.9 years. Familial history for BD was present in 32 (9.7%) of the patients and a familial history of oral aphthous ulcer was present in 74 (22.5%) of the patients. While BD initiated at an average age of 25.2 years in males, the females started suffering the disease at the age of 23, on average. The disease, thus, started at an earlier age in females compared to in the males (p<0.05). The average age of diagnosis was 33.1 years in males and 31.4 years in females (p>0.05).

Behçet’s disease was found to have an earlier onset in individuals with a positive familial history of oral aphthous ulcer or BD (p=0.03 and p=0.02, respectively).

Initial finding of Behçet’s disease
In 95.4% (n=314) of the patients, the finding that was initiated first was repetitive oral aphthous ulcerated lesions, while on the other hand, the initial finding was genital ulcers in 13 patients and ocular involvement in 2 patients.

Clinical findings of Behçet’s disease

Oral aphthous ulcers and genital ulcers
Oral aphthous ulcers were noted in the entire set of patients. The proportion of genital ulcers was 82% (n=163) in males and 87% (n=113) in females (p=0.213).

Ocular involvement
Ocular involvement was found to exist in 122 (37.1%) of the patients. Ocular involvement was more common in males (p=0.014). Repetitive anterior uveitis, posterior uveitis, retinal vasculitis, optic atrophy, and panuveitis were considered as ocular involvement. We identified that 27 patients had anterior uveitis, 21 had posterior uveitis, 3 had retinal vasculitis, 1 had optic atrophy, and 1 had panuveitis.

HLA-B51 antigen
The HLA-B51 antigen could only be studied in 179 patients and was positive in 79 (44.1%) of them. Out of the positive patients, 38 (38.8%) were males and 41 (50.5%) were females (p=0.103).

Pathergy testing
Pathergy testing was conducted on 277 patients. Among them, the pathergy test was concluded to be positive in 135 (48.7%) patients. The test results were positive in 86 (63.7%) male and 49 (36.2%) female patients, which did not amount to a significant difference (p=0.316).

Papulopustular lesions and erythema nodosum (EN)
Papulopustular lesions were observed in 230 (69.9%) patients, comprising 144 (62.2%) males and 86 (37.4%) females. The difference was not significant (p=0.235). EN was detected in 95 (28.9%) patients, 53 (55.7%) of whom were males and 42 (32.3%) females. No difference was determined in terms of gender (p=0.272).

Joint involvement
In our sample of patients with BD, 189 (57.4%) had arthritis or arthralgia. Among those patients, 98 (51.8%) were males and 91 (48.1) were females. Joint problems were more frequent in women than in men to a significant extent (p<0.001). Joint involvement was found to be higher in individuals with EN (p=0.02).

Vascular involvement
Among the patients with BD, 109 (33.1%) patients, of whom 89 (81.6%) were males, had vascular involvement. The vascular involvement was significantly higher in males than in females (p<0.001). Thrombophlebitis was detected in 23 (7%) patients, deep vein thrombosis (DVT) in 62 (18.8%), vena cava inferior syndrome (VCIS) in 6 (1.8%), vena cava superior syndrome (VCSS) in 6 (1.8%), Budd-Chiari syndrome in 3 (0.9%), pulmonary artery aneurism in 6 (1.8%), and femoral artery aneurism in 3 (0.9%).

Neurological involvement
A total of 25 (7.6%) patients, comprising 17 males and 8 females, had Neuro-Behçet’s disease (with vascular or parenchymal involvement). This difference by gender was not significant (p=0.409). When it comes to headache, 150 (45.6%) patients had headache, 78 (52%) of whom were females. Headache was more significant in women, exhibiting a significant difference (p<0.001).

The breakdown of clinical findings according to the genders is given in Table 1.

Discussion
Behçet’s Disease is a multi-system vasculitis affecting young adults. Gender has an impact on its clinical findings and prognosis. A review of

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Patients n (%)</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral aphthous ulcer</td>
<td>329 (100)</td>
<td>199 (100)</td>
<td>130 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>276 (84)</td>
<td>163 (82)</td>
<td>113 (87)</td>
<td>0.213</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>122 (37.1)</td>
<td>84 (42.2)</td>
<td>38 (29.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Erythema nodosum (EN)</td>
<td>95 (28.9)</td>
<td>53 (26.6)</td>
<td>42 (32.3)</td>
<td>0.272</td>
</tr>
<tr>
<td>Papulopustular lesions</td>
<td>230 (69.9)</td>
<td>144 (72.4)</td>
<td>86 (66.2)</td>
<td>0.235</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>109 (33.3)</td>
<td>89 (44.7)</td>
<td>20 (15.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neuro-Behçet’s disease</td>
<td>25 (7.6)</td>
<td>17 (8.5)</td>
<td>8 (6.1)</td>
<td>0.409</td>
</tr>
<tr>
<td>Headache</td>
<td>150 (45.6)</td>
<td>72 (36.2)</td>
<td>78 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Joint involvement</td>
<td>189 (57.4)</td>
<td>98 (49.2)</td>
<td>91 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathergy test positivity*</td>
<td>135 (48.7)</td>
<td>86 (52.4)</td>
<td>49 (34.3)</td>
<td>0.316</td>
</tr>
<tr>
<td>HLAB-51 antigen Positivity**</td>
<td>79 (44.1)</td>
<td>38 (38.8)</td>
<td>41 (50.6)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

BD: Behçet’s disease
*Pathergy testing was conducted on 277 patients
**HLAB-51 tissue type could only be studied in 179 patients
a series of study reports published in various countries reveals the variance in gender distribution of the disease by country. Accordingly, the male/female ratio is 0.63 in Korea, 0.98 in Japan, 1.3 in Iran, and 1.34 in China, while two studies from Turkey report levels of 1.3 and 1.15. In a similar manner with the literature data, in our study, this level was calculated to be 1.53 (3-8). The age of disease onset in BD is 25.8 in Azerbaijan, 28.3 in Iran, 29 in China, 29 in Korea, and 25.6 years in Turkey based on the 1997 study of Gürler et al. (7) (3, 5, 6, 9). In our study, the age of onset was 24.3 years. The differences may arise from the different patient inclusion criteria and regional variances. Although the literature does not indicate any difference by gender in the age of disease onset, we determined an earlier onset of BD in our female patients.

Despite the reason behind BD remaining elusive, the importance of familial history is highlighted in the literature concerning the genetic predisposition (12). A positive familial history in BD has been reported to be as high as 15.4% in an epidemiological study by Bang et al. (3) in Korea, while it is as at the level of 3.9% in Iran and 2% in Japan; and in Turkey, it was determined to be 7.3% in the analysis of Gürler et al. (7), 13.3% in the analysis of Uğurlu et al. (8), and finally, 9.7% in our patients (4, 10). Patients with BD also have an increased frequency of oral aphthous ulcers independent of a familial history of BD. In our study, the frequency of occurrence of oral aphthous ulcers in the family was 22.5%. This figure is close to the proportion detected in Iran, i.e., 28.5–29.2% (10). Moreover, we identified an earlier onset in patients who have a positive familial history of BD and likewise in patients who have a positive familial history of oral aphthous ulcers, a conclusion that was not mentioned in other studies.

As per the 1990 International Study Group, all patients should have recurrent oral aphthous ulcers so that they can be diagnosed to have BD (11). Indeed, all of our patients had an oral aphthous ulcer. Indeed, in most of the cases, the initial finding of the patients is established to be oral aphthous ulcer. Consistently, the initial finding of BD was oral aphthous ulcer in 95.4% of our patients. The initial finding was rarely genital ulcers and ocular involvement, which is in line with the available literature (3, 4, 8).

There are studies in the literature that imply a difference in clinical findings between male and female patients, but there are also other studies that fail to demonstrate such a difference (3, 5, 7-10).

Ocular involvement ranged between 32.9% and 58.1% in the evaluated studies (5, 8). Ocular involvement in our patients was similar to that in the literature, and males had a greater rate of ocular involvement, similar to the study of Uğurlu et al. (8).

In another study conducted in Turkey, HLA-B51 antigen positivity frequency was, similarly to our study, stated to be around 44% (8). The frequency of a positive pathergy test result varied among the studies. Certain studies concluded an elevated level of positive results in males (10). Gürler et al. (7) reported 56.8% of the patients were positive in the pathergy test, whereas Uğurlu et al. (8) stated this proportion as 40.8%, while a study from Japan reported a figure of 43.8% (4). However, there was no difference among our male and female patients in terms of positive pathergy test results.

In their study, Uğurlu et al. (8) reported a higher proportion of EN and joint involvement in women. Despite EN being found to occur more commonly in our female patients, as also described by the current literature, this difference was not significant. The higher occurrence of joint involvement in females, on the other hand, was at a significant extent. Some clinical features of BD tend to manifest jointly (2). Although the concurrence of joint involvement and papulopustular lesions has been defined in the literature, we identified joint involvement to be more common in those with EN.

In BD, the vascular involvement is not only a widespread involvement type but is also determinative in disease prognosis. The prognosis of BD in male patients becomes worse particularly in the event of ocular involvement, neurological involvement, or vascular involvement (2). In agreement with the study of Uğurlu et al. (8), we found vascular involvement and ocular involvement to be more common in males. In their study, Davitchi et al. (10) could not specify a strong correlation between the major symptoms of BD and gender, yet the strongest correlation was attributed between the vascular involvement and male gender. Uğurlu et al. (8) found that disease severity and prognosis were worse in men at BD patients. The aim of our study was not to determine the severity of the disease or prognosis; however, we did find that vascular and ocular involvement occurred more common in men in our study. From a gender-oriented point of view, certain studies demonstrate a higher prevalence of neurological involvement in males (8). Although neurological involvement was more common in males in our study as well, the difference was not significant. Actually, the most common manifestation of neurological involvement in BD is headache (13). Our patients suffered headache at a proportion of 45.6%, which corresponds to a higher figure given the proportions in the literature, and, in compliance with the literature data, headache was more commonly encountered in women than in men (5). It is difficult to speculate whether or not headache has a direct association with the BD, as it has not been classified.

The key limitation of our study was its retrospective design. Another main limitation was the fact that neither HLA-B51 antigen nor pathergy testing could be performed on all our patients.

In conclusion, the clinical features of BD may vary between the genders. Variations exist in the results depending on the size of the examined population, the department where the study was conducted, patient inclusion criteria, and also the region where the patients are living. In particular, similar to the previous literature, vascular involvement and ocular involvement were found to be more common in our male patients, whereas joint involvement was detected to occur more frequently in female patients. During the follow-up of patients with BD, these results should be kept in mind regarding the monitoring and prognosis of the disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskişehir Osmangazi University School of Medicine.

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

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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