THE EFFECTS OF EPIDEMIOLOGICAL AND CLINICAL FINDINGS IN BEHÇET’S DISEASE ON THE COURSE AND PROGNOSIS OF THE DISEASE

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Introduction

Behçet’s disease (BD) was first defined in 1937 by the Turkish dermatologist Dr. Hulusi Behçet as a syndrome generated by recurrent oral aphthae (OA), genital ulcer (GU) and iridocyclitis with hypopyon. To date, BD is defined as a chronic, recurrent vasculitis that has numerous clinical symptoms, and articular, vascular, gastrointestinal system, pulmonary system, cardiovascular system, renal and central nervous system findings along with mucocutaneous and ocular findings14. Since there is no specific laboratory finding, it is diagnosed based on clinical findings. The criteria established by the International Behçet Disease Study Group are the principal diagnostic criteria5. The fact that the disease is frequently seen in the countries on the historical Silk Road indicates that genetic and/or environmental factors may have a role in the progress of the disease. In the aforesaid geographical area, Turkey is the country in which the disease is most commonly seen6.

The disease generally develops late in the second decade of life, and is mostly seen between the ages of 20 and 40. It has more severe clinical manifestations in males. Death generally occurs depending on the degree of gastrointestinal system (GIS) involvement and neurologic involvement which may cause perforation and major vascular involvement like pulmonary artery aneurysm7-9.

ABSTRACT

Aim: Behçet’s Disease (BD) is a complex disease which occurs as a result of the involvement of different systems. In this study, we aim to determine the importance of clinical findings and demographic data in its occurrence and in understanding the prognostic importance of BD, and to establish the influencing factors of these findings.

Materials and methods: We conducted a retrospective statistical analysis on the clinical and demographic data assessed by examining the patient charts of 703 patients with BD who were admitted to the Behçet outpatient clinic in Erciyes University Department of Dermatology between 1998 – 2010.

Results: Seven hundred and three patients were included in this study, of which 297 (42.2%) were male, and 406 (57.8%) were female. The mean age at diagnosis of the disease was 30.1±19.1 years. Mucocutaneous findings were the most frequent and first seen findings of the disease. The most frequent finding after mucocutaneous ones was ocular involvement. It was observed that vascular involvement was more common in male patients compared to female ones. In contrast, genital ulcer, erythema nodosum and arthralgia were seen more in female patients than in males.

Conclusion: There is not a specific laboratory, monitoring or histopathologic examining method for the diagnosis and assessment of the prognosis of the disease. Consequently, it seems that the age, gender, genotype and other existing clinical findings of the patient give a clue to the prognosis of the disease.

Key words: Behçet’s disease, clinical findings, demographic data.

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It is thought that its etiopathogenesis is multifactorial. In previous studies it was shown that genetic factors, infectious agents, immune alterations, oxidative stress, lipid peroxidation and environmental factors have a role in its etiology\(^9\).

BD does not present with similar symptoms and findings in every patient and in all areas. In this study, we aim to determine the importance of clinical findings and demographic data of our country in its occurrence and in understanding the prognostic importance of Behçet’s diseases, and to establish the influencing factors of these findings.

**Materials and methods**

This study was conducted between 1998 and 2010 at the Department of Dermatology of Erciyes University Hospital. The Ethics Committee of Erciyes University Faculty of Medicine approved the study protocol.

Seven hundred and three patients with BD who were admitted to the Behçet outpatient clinic in Erciyes University Department of Dermatology, constituted our study group. Their diagnosis was made according to the International Behçet Disease Study Group Diagnostic Criteria\(^5\).

The existing symptoms and physical examination findings of the patients were recorded. The starting time and frequency of each clinical symptom were recorded, and these changes in these findings were questioned and noted down at each check up. For each patient laboratory examination (erythrocyte sedimentation rate (ESR), c-reactif protein (CRP), Antistreptolizin O (ASO), complete blood count and biochemical tests) and pathergy test were conducted, and the results were recorded. Ophthalmological check-up and examinations were done for each patient.

Mean, standard deviation, frequency and ratio values were used as descriptive statistics for data. Distribution of the data was analyzed by using the Kolmogorov - Smirnov test. T test was used for parametric quantitative data, and Mann-Whitney U test was used for nonparametric data analysis. In the analysis of proportional data the chi-square test was used; in cases in which chi-square conditions were not met, the Fisher test was used. In the correlation analysis of the variables, Pearson and Spearman correlation analysis were done based on the type of the variable. Tests were done in the confidence interval of 95%. The SPSS 19.0 Windows (Statistical Packages for Social Sciences; SPSS IBM Corporation) statistical program package was used in the analysis of the data. The means are shown as mean ± std. dev. P values under 0.05 were considered statistically significant.

**Results**

Fourteen patients (26.9%) received thrombolytic. Seven hundred and three patients who were admitted to the Behçet outpatient were included in our study, of these 297 (42.2%) were male, and 406 (57.8%) were female. The male/female ratio was 0.73. The mean age at diagnosis of the disease was 30.1±19.1 years. While the mean age at diagnosis for female patients was 29.9±19.9 years, it was detected as 30.3±17.9 years for males (Table 1). The youngest patient was diagnosed with the disease at the age of 5, and the oldest was 65 when he was diagnosed. There was no significant difference among age groups according to gender ratios.

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>0-16 years</th>
<th>17-50 years</th>
<th>&gt;50 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n / %</td>
<td>n / %</td>
<td>n / %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 / 37.80%</td>
<td>271 / 42.90%</td>
<td>5 / 26.3</td>
<td>0.295</td>
</tr>
<tr>
<td>Female</td>
<td>28 / 62.20%</td>
<td>361 / 57.10%</td>
<td>14 / 73.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Number of patients based on age groups.

The most frequent initial finding was oral aphthae (OA) (72.7%). Genital ulcer (GU), erythema nodosum, and ocular involvement were within the initial findings with percentages of 7.3%, 3.8% and 1.6% respectively. In 11.8% of the patients GU and OA started at about the same time (Table 2).

<table>
<thead>
<tr>
<th>Initial finding</th>
<th>n / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral aphthae</td>
<td>511 / 72.7</td>
</tr>
<tr>
<td>Oral aphthae + genital ulcer</td>
<td>83 / 11.8</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>51 / 7.3</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>27 / 3.8</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>11 / 1.6</td>
</tr>
<tr>
<td>Other</td>
<td>20 / 2.8</td>
</tr>
<tr>
<td>Total</td>
<td>703 / 100</td>
</tr>
</tbody>
</table>

Table 2: Initial symptoms of the patients.

Mucocutaneous involvement represents the most frequent symptoms in the patients. The percentages of frequency for OA, GU, erythema nodosum...
(EN), acne-like lesions and positivity of pathergy were 100%, 82.6%, 42.8%, 52.8% and 13.7% respectively. As the onset age of any OA, GU and EN decreases, the onset age of others decreased as well.

In male patients, the frequencies of extragenital ulcer (M:4.0% F:0.7%; p = 0.021), superficial thrombophlebitis (M:9.8% F:3.0%; p=0.000), venous insufficiency (M:3.4% F:0.2%; p=0.001), acneiform eruption (M:61.6% F:46.3%; p=0.000), ocular involvement (M:41.8% F:21.4%; p=0.000) and major vascular involvement (M:5.4% F:2.5%; p=0.042) were statistically significantly higher in comparison with female patients (p<0.05). In female patients the frequencies of GU (M:78.8% F:85.5%; p=0.021), erythema nodosum (EN) (M:63.4% F:47.5%; p=0.003) and arthralgia (M:65.3% F:75.6%; p=0.003) were statistically significantly higher in comparison with male patients (p<0.05). There was no significant difference between male and female patients in terms of the frequency of smoking, BD family history, OA, OA in family, arthritis, neurologic involvement, GIS involvement, chest involvement and pathergy (p>0.05).

There was no significant difference between patients over 50 and 17-50 years in terms of the frequencies of OA, GU, EN, acneiform eruption, arthritis, arthralgia, DVT or family history (p>0.05). In patients in the 0-16 age group the frequencies of GU, EN, acneiform eruption and arthralgia were statistically significantly lower than those in the 17-50 age group (p<0.05) (Figure 1).

One hundred and five patients had a family history (15%). Of these, 64.8% had a BD history in first degree relatives, 8.6% had it in second degree relatives and 21% of them had it in third degree relatives. OA history in patients who had a BD family history was higher (p<0.05). There was an OA family history in 55.6% of the patients. The OA onset age in the patients who had an OA family history (23.7±18.7) was statistically significantly lower than in those who did not (26.2±18.4) (p<0.05).

There was GU in 581 patients (82.6%). The mean genital ulcer onset age was 28.1±17.8 years. The mean onset age in females was found as 27.7±9.2, and in males it was 28.7±8.3. GU was most frequently localized at scrotum (93.3%) in males and at labium majus (96.8%) in females.

There were extragenital ulcers in 2.2% of the patients. These were localized in the inguinal region, leg, breast and anal region. Extragenital ulcer incidence was seen to be statistically significantly higher in patients with superficial thrombophlebitis and venous insufficiency (p=0.000<0.001).

![Table 3: Ocular involvement percentages in patients with genital ulcer.](image)

Ocular involvement ratios were compared between the patients with and without GU. GU was seen statistically significantly lower in the patients with ocular involvement (131 patients; 62.1%) than the ones without it (450 patients; 91.5%) (p=0.000<0.001) (Table 3). No relationship was found between genital ulcer and other findings.

There were extragenital ulcers in 2.2% of the patients. These were localized in the inguinal region, leg, breast and anal region. Extragenital ulcer incidence was seen to be statistically significantly higher in patients with superficial thrombophlebitis and venous insufficiency (p=0.000<0.001).
EN was found in 42.8% of the patients. The mean onset age of EN was 29.5±19.5 years. Superficial thrombophlebitis, arthralgia and arthritis frequencies were statistically significantly higher in patients with EN than in those without (p<0.05) (Table 4).

Papulopustular lesions were present in 52.8% of the patients. They were often localized on the dorsum, breast, leg and hips. These lesions were observed more often in smoking patients when compared the nonsmokers(p<0.05).

There was ocular involvement in 30% (n: 211) of the patients. Anterior uveitis was present in 73.5%, posterior uveitis in 5.2%, panuveitis in 3.3%, vitritis in 3.3% and retinal vasculitis in 1.4% of these patients. Less papillitis, macular degeneration, cataract, retinal detachment, optic neuritis, optic atrophy and glaucoma were observed. In 26.5% of the patients with ocular involvement permanent and partial vision losses were present. The onset age of ocular involvement was observed as 28.8±19.1 years (27.7±10.3 in females), (29.5±8.8 in males). In 1.6% of the patients eye complaints appeared as the first finding. The most frequent symptoms of ocular involvement were vision loss with an incidence in 45.5%, eye redness with 30%, sudden vision loss with 10% and pain with 6%. In 26.5% of our patients with ocular findings there was post-attack partial or permanent vision loss. The number of attacks in the eye was compared between the patients with vision loss and those without it.

Table 4: Percentages of superficial thrombophlebitis, arthralgia and arthritis frequencies in patients with erythema nodosum.

<table>
<thead>
<tr>
<th></th>
<th>Erythema nodosum</th>
<th></th>
<th></th>
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<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Existing</td>
<td>Not existing</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n / %</td>
<td>n / %</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Superficial thrombophlebitis</strong></td>
<td>(-)</td>
<td>392 / 59.2%</td>
<td>270 / 40.8%</td>
<td>662</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>10 / 24.4%</td>
<td>31 / 75.6%</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>(-)</td>
<td>138 / 68.3%</td>
<td>64 / 31.7%</td>
<td>202</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>264 / 52.7%</td>
<td>237 / 47.3%</td>
<td>501</td>
<td></td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>(-)</td>
<td>366 / 59.2%</td>
<td>252 / 40.8%</td>
<td>618</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>36 / 42.4%</td>
<td>49 / 57.6%</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>402 / 57.2%</td>
<td>301 / 42.8%</td>
<td>703</td>
<td></td>
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</tr>
</tbody>
</table>

The number of attacks in the patients with vision loss was statistically significantly higher than in those without it (p=0.000<0.05). In patients with GU, ocular involvement was observed less. Apart from that, no relationship was detected between ocular involvement and other findings.

Arthralgia was present in 71.3% of the patients. Arthritis, superficial thrombophlebitis, DVT and venous insufficiency were observed with rates of 12.1%, 5.8%, 4.3% and 1.6% respectively. The percentage of major vascular involvement was 3.7%. Main femoral vein thrombosis (0.5%), sinus vein thrombosis (0.7%), main iliac vein (0.1%), vena cava superior (0.1%), portal vein (0.1%), saphena vein and jugular vein thrombosis (0.1%) were included in major vascular involvement; there was also aneurysm in the pulmonary artery (0.3%) and aorta (0.1%).

EN was statistically significantly higher in patients with arthralgia and arthritis (p<0.05). No relationship was found among arthralgia and other symptoms and findings.

DVT and venous insufficiency frequencies between patients with superficial thrombophlebitis and those without it were compared by using the chi-square test. There was a statistically significant higher frequency of superficial thrombophlebitis in patients with DVT (9 patients; 30%) than in those without it (32 patients; 4.8%) (p=0.000<0.001). There was a statistically significant higher frequency of superficial thrombophlebitis in patients with venous insufficiency (4 patients; 36.4%) than in those without it (37 patients; 5.3%) (p=0.002<0.001).

The DVT presence frequency and major vascular involvement ratio were compared by using the chi-square test. There was a statistically significant higher frequency of major vascular involvement in patients with DVT (7 patients; 26.9%) than in those without it (19 patients; 73.1%) (p=0.000<0.05)

GIS BD was detected in only 2 patients, while GIS symptoms were present in 67 patients. The most frequent GIS symptoms were constipation, abdominal pain, nausea and diarrhea. It was thought that these symptoms were caused by treatment. Two patients with GIS involvement had a positive family history for BD.

There was neurological involvement in 17 patients (2.4%). Ten of these patients were male, while 7 of them were female. In addition headache was observed in 203 patients (28.9%). At the end of the examination of these patients migraine, tension
type headache and intracranial mass were detected in 8, 4, and 1 patient respectively. The mass was not related to BD. No relationship was determined between neurological involvement and other findings.

Pulmonary involvement, which is one of the rarely seen systemic findings, existed in 3 patients (0.4%). It was determined that extragenital ulcer, superficial thrombophlebitis, venous insufficiency and major vascular involvement were higher in these patients (p<0.05).

During our follow-ups, mortality was observed in two male patients. There was thrombosis in the vena cava in one of these patients, and neurological involvement and vasculitis in the capsula interna existed in the other patient.

Eleven female patients who were diagnosed with BD got pregnant during the follow-ups. All treatments were ceased for these patients. In one patient, thrombosis in the femoral vein developed after pregnancy. No complication or increase in severity of disease was observed during or after pregnancy in other patients.

Discussion

Numerous researchers in several disciplines have studied BD, and many studies have been done about the epidemiology, clinical course, pathogenesis, genetics, immunology and treatment of the disease since it was first defined in 1937 by Prof. Dr. Hulusi Behçet. Although much valuable immunological, genetic and serologic research has been done, no exact guiding parameter has been produced for the diagnosis and follow-up of the disease. Therefore, the clinical findings of patients seem to be the most important factor in the diagnosis, prognosis, and even the determination of treatments. The fact that our study was conducted from a single center, and the patients were evaluated by the same clinician is the advantage of our study in comparison with other similar ones.

It is known that the disease is mostly seen, and has a more severe clinical course in males. In the studies done in the United States of America, Korea and Brazil, female predominance was shown, and it has been observed that the male/female ratio has been decreasing in recent years. In our study, the disease was more common in women as well as starting at an earlier age. Starting at an earlier age and being more common could not be associated with the severity of the disease.

In our study, systemic involvements were observed more in males. Moreover, statistically significant higher rates of vascular and ocular involvements were observed in males. Similarly to our study, in the study of Gürler et al. with 2147 BD patients, it was shown that ocular, neurological and vascular involvements were higher in males.

While the clinical findings in childhood are similar to those in adults, it was stated that serious organ involvements might be more common in children. Sarica et al. reported 95 cases of juvenile onset BD in the 1784 BD patients they analyzed. In that study, 51 of the cases were male, and 44 of them were female. It was stated that systemic involvement was observed in the first 5 years. Borlu et al. analyzed 17 children aged between 4 and 16, and they detected a positive family history in 47% of the cases. In the retrospective study of Hamzaoui et al. the clinical findings of BD were compared between patients younger than 20 (n=81) and those older than 40 (n=68). They observed that cutaneous involvement and vena cava thrombosis were more frequent in the <20 age group, and the frequency of joint involvement was higher in the >40 age group. In our study 45 patients were diagnosed before 16 years of age. In these patients, lesions were fewer and milder in comparison with those in the 17 - 50 age group. Furthermore, no difference was determined between other groups in terms of family history in juvenile cases.

It was reported that in familial BD the disease was more severe, and a high incidence of ocular, skin, joint and neurological involvements existed. While there was more family history of OA in the patient with a family history of BD, no relationship was shown between other disease findings. This situation makes us think that there must be other factors influencing the development and prognosis of the disease besides genetic factors.

Our study indicates that oral ulcers are the most prevalent onset manifestations of patients and the disease is often diagnosed with a delay of several years after the appearance of this onset sign. There is no way of predicting whether or not a patient with recurrent oral ulcerations will develop BD. Therefore careful examinations of patients, including their minor symptoms, additional laboratory tests, and regular follow-ups by physicians are required for proper diagnosis and prognosis of BD.

The fact that arthralgia is more frequent in BD indicates that the joints are one of the target organs in BD, just like in most systemic diseases.
Although joint problems in the form of arthritis and arthralgia are not included in the International Study Group Criteria, they are symptoms seen in most patients. The frequency of arthritis in prospective studies varies between 40% and 70%, and is higher in males\(^\text{(7)}\). In previous studies it was stated that acneiform lesions were more frequent in patients with arthritis\(^\text{(16)}\). However, no relationship was observed in these two findings in our study. Nevertheless, we observed that erythema nodosum was more common in patients with arthritis and arthralgia.

The positivity rates of pathergy test in Behçet’s disease show ethnic differences\(^\text{(9)}\). While correlation studies of the pathergy test with disease activity are not sufficient, Davies et al. showed that positive pathergy test has no correlation with the clinical symptoms of BD. On the other hand, Koç et al. reported that it might be associated with vascular involvement\(^\text{(21)}\). In our study, we found a pathergy positivity rate of 13.7%. In our study, no relationship was found between pathergy positivity and other findings of BD. Regularly repeating the pathergy test at patient follow-ups may increase the positivity rate, and help to reveal whether or not it has a relationship with other findings. Additionally, removing the differences in application techniques of the pathergy test, and developing a standard method would help us to understand its importance in disease prognosis.

Extragenital ulcers are seen in 3% of patients, but they are quite characteristic lesions for the disease\(^\text{(20)}\). In our study extragenital ulcers existed in 2.2% of our patients. A higher ratio was detected in males. These were localized in the inguinal region, leg, breast and anal region. Extragenital ulcers were observed more in patients with superficial thrombophlebitis and venous insufficiency. The fact that GU and extragenital ulcers were not associated statistically significantly supports the idea that other factors may have a role in the development of these two findings.

In Behçet patients, EN lesions are seen with ratios varying from 47.6 - 55.3%, and are observed more in females\(^\text{(8)}\). In line with the literature, erythema nodosum was observed more in females in our study. Nevertheless, superficial thrombophlebitis, arthralgia and arthritis had a higher prevalence in Behçet patients with EN in comparison to those without it. Also, thrombophlebitis is more frequent in patients with venous insufficiency and DVT, and these two findings are seen in males more. On the basis of this information, it might be assumed that vascular incidents like venous insufficiency, superficial thrombophlebitis and DVT might be seen more in patients with EN.

In previous studies, the ocular involvement ratio in patients with BD is around 50%. While this ratio increases in young and male patients, it decreases to 30% in older and female ones. Again, studies based on hospital data showed that ocular involvement starts in the first couple of years in the course of the disease, and as disease age increases the ratio of ocular involvement onset decreases\(^\text{(22)}\). Thirty percent of our patients had ocular involvement. Only for 1.6% of the patients was ocular involvement the first finding. The reasons for lower ocular involvement ratios in comparison with other studies might be due to the following reasons; starting systemic treatment once the patients were diagnosed, following up the patients in the discipline of dermatology, and the fact that majority of our patients were female. Again, we observed that the frequency of ocular involvement and the number of attacks decreased as age increases. Our study shows that attack frequency is one of the most important factors in the development of vision loss, and shows the importance of decreasing the number of attacks with early and effective treatment for the prevention of permanent morbidities. In our study, we observed lower GU and other mucocutaneous findings in patients with ocular involvement. We did not observe any similar statistical evaluation in the literature.

Inflammation liability in large, medium and small veins in both the arterial and venous systems and also the liability of thrombosis in the lumen of the vein are observed in BD\(^\text{(23)}\). Vascular involvement in BD shows ethnic differences. Up to now, the series with the highest number of vascular involvements was reported in Algeria (62%), and the lowest number of vascular involvements was reported in Japan\(^\text{(23,26)}\). Major vascular involvements include thrombosis in the femoral vein, transverse sinus, main iliac vein, vena cava superior, portal vein, saphena vein and jugular veins, and pulmonary artery and aneurysm in the aorta. Vascular involvement was present in the patients who developed mortality. Therefore, this proves that vascular involvement is one of the most important determinants in the prognosis of the disease.
Conclusion

BD, which was defined as a triple complex by Prof. Dr. Hulusi Behçet, today confronts us as a systemic disease that may affect several organs and systems. Because there is not a standard approach to determine the prognosis of the disease, analyzing the demographic data, clinical findings and variations of patients, and revealing possible relationships among them still seem to be the best approach to gain information about the prognosis of the disease.

References