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# Clinical Manifestations in Behçet's Diseased Patients: Is It Affected by Disease Activity?

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## ABSTRACT

**Background:** Behçet's disease (BD) can affect both tiny and large blood vessels. However, there are scant reports on the relationship between clinical features and illness progression in Egyptian BD patients. **Objective**: To examine the connection between clinical symptoms and disease progression in patients diagnosed with Behçet's disease.

**Patients and methods:** A total of 36 BD patients were included in the current study. They were all diagnosed in accordance with the International Study Group for Behçet's Disease criteria and recruited from the outpatient clinics and inpatient Department of Rheumatology, Rehabilitation, and Physical Medicine at Assiut University Hospital, Egypt. Disease activity was assessed using Behçet's Disease Current Activity Form (BDCAF). The patients were categorized into two groups, 18 with active BD and 18 with inactive BD, using the BDCAF. Medical history and physical examination were done for all participants in the study.

**Results:** The median age of the studied participants was 37 years (range 20-52 years), with high male predominance as we found that, out of 36 studied BD patients; 30 (83.3%) were males and 6 (16.7%) were females. Median BDCAF was 4 (range 2–5). Mouth ulceration, arthritis, and arthralgia were the most common clinical manifestations among the studied cases documented in 18 (50.0%) cases, followed by headache in 15 (41.7%) cases, then genital ulceration in 14 (38.9%) cases, and red painful eye in 14 (38.9%) cases. Muco-cutaneous manifestations (mouth and genital ulcerations), erythema, blackout, and active CNS events were more prevalent among patients with active BD ($P<0.05$, for all).

**Conclusion:** Clinical manifestations may be useful indicators of Behçet's disease progression, according to the results of the current investigation. Mucocutaneous, ocular, and central nervous system symptoms, as well as disease activity, may indicate a poor prognosis.

**Keywords:** Behçet's diseased, Clinical manifestations, Disease activity.

## INTRODUCTION

Behçet's disease (BD) is a rare, life-threatening vasculitis that can affect both large and small arteries and veins, resulting in a wide range of clinical manifestations [1]. BD typically manifests itself between the ages of 30 and 40, and its prevalence may be equal between the two sexes or may be more common in men [2].

The main clinical presentations of BD are recurrent mouth and genital ulcerations in addition to ocular involvement [3]. Skin abnormalities such as erythema nodosum, papulopustular eruptions, cutaneous vasculitis, and a positive pathergy test result are other possible skin presentations of Behçet's illness [2], articular, neurological manifestations [4], vascular , urogenital [5], pulmonary as well as intestinal presentations [6]. It is important to note that Behçet's disease is a separate clinical entity from other similar conditions, and there are regional variations in how it manifests. Individuals from the United States and Northern Europe are more likely to experience central nervous system involvement, while Japanese patients are more likely to experience gastrointestinal symptoms. Geographic variation is also seen in the progression rate, frequencies of the various symptoms, and also associated with the HLA-B51. Patients from Japan and the Mediterranean region have more severe conditions and a stronger correlation with HLA-B51 [7].

The natural course of BD is mainly acute with frequent recurrence, the degree of various organs involvement lead to variable disease activity and outcome [1]. Behçet's disease mortality rates can be anywhere from 0.9% and 10%; the disease's neurological symptoms and major organ vasculitis are the primary causes of death [8].

The objective of this study is to examine the connection between clinical symptoms and disease progression in patients diagnosed with Behçet's disease.

## PATIENTS AND METHODS

### Study Design and Setting

At the Rheumatology, Rehabilitation, and Physical Medicine Department at Assiut University Hospital in Assiut, Egypt, we conducted this comparative cross sectional study.

### Study Population

Patients with BD who met the Revised International Criteria for Adamantiades-disease Behçet's [9]. All eligible patients, admitted to the aforementioned hospital between September 1, 2018 and April 30, 2019, were invited to participate in the study. Patients who met the Revised International Criteria for Adamantiades-illness Behçet's and were 18 years old and of either sex were considered eligible for participation in our study [9], that characterized by frequent instances of ulcers of mouth (2 point),



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recurrent genital ulceration (2 points), eye lesions (2 points), skin lesions (1 point), vascular lesions (1 point), and positive pathergy test (1 point); the diagnosis was confirmed in a patient with three or more points. Patients whose final diagnoses were inconclusive for BD were disqualified, as well as those who declined to take part in the study.

**Data Collection and Assessment**

Eligible patients underwent a comprehensive history and physical examination that included the identification and classification of cutaneous manifestations according to lesion type and location as well as extra-cutaneous manifestations. Vascular, neurological, ocular, articular, gastrointestinal, and cardiac manifestations were collected and analyzed. As a result of these clinical evaluations, all BD patients were placed into one of two categories: active or inactive.

**Disease activity**

Simplified versions of Behçet's Disease Current Activity Form were used to evaluate disease activity [9, 10]. It needs the presence of at least two of the following symptoms to diagnose active Behçet disease: Thrombosis, thrombophlebitis, skin lesions, arthritis, neurological involvement, or genital and oral ulcers.

**Ethical considerations:**

**An approval of the study was obtained from Medical Ethics Committee at Assiut University. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical Analysis***

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). When applicable, data were statistically described using the median, range, frequencies (number of cases), and relative frequencies (percentages). In order to compare quantitative factors, the Mann Whitney test was utilized. The Chi-square ($X^2$) test was used to compare the two sets of categorical information. When the anticipated frequency was less than 5, a Fisher's exact test was applied instead. P value $\leq 0.05$ was considered significant.

**RESULTS**

Participants mean age was 37 years, ranged from 20 to 52 years old. Out of 36 BD studied cases; 30 cases (83.3%) were males versus six cases (16.7%) were females, with male to female ratio was nearly 5:1. The median BDCAF was 4 and ranged from 2 to 5. In terms of age and sex, there was no discernible difference between patients with active and inactive BD (P value 0.650 and 0.658, respectively), as shown in Table 1.

**Table (1): Demographic data and disease activity of Behçet's diseased patients**

| Demographic data | Total (n=36) | | Active BC (n=18) | | Inactive BC (n=18) | | P-value |
|---|---|---|---|---|---|---|---|
| **Age (years), median (range)** | 37 (20 – 52) | | 34 (20 – 52) | | 40 (23 – 44) | | 0.650 |
| **Sex, n (%)** | | | | | | | |
| • Female | 6 | (16.7) | 2 | (11.1) | 4 | (22.2) | 0.658 |
| • Male | 30 | (83.3) | 16 | (88.9) | 14 | (77.8) | |
| **BDCAF, median (range)** | 4 (2 – 5) | | | | | | |

Quantitative data are presented as median (range), qualitative data are presented as n (%). *Significance defined by $p \leq 0.05$.

Based on BDCAF, the patients were subdivided into 18 patients with active BD, and 18 patients with inactive BD. The clinical manifestations affecting the whole BD studied patients and the comparison of these clinical manifestations among patients with active and inactive BD were presented in Table 2.

The most common clinical manifestation was mouth ulceration, arthritis, and arthralgia in 18 cases (50.0%), followed by headache documented in 15 cases (41.7%), then genital ulceration, red painful eye in 14 cases (38.9%), blackout in 12 cases (33.3%), erythema, and active CNS events in eight cases (22.2%), skin pustules, diarrhea, blurred double vision, chest pain and hard breathing were documented in four cases (11.1%), nausea and vomiting, cough of blood, leg pain in two cases (5.6%), and none had neurological manifestations in the form of difficult speech & hearing, weakness of face, arms, or legs, memory loss, or loss of balance. And by comparing the above mentioned clinical manifestations among patients with active or inactive BD we observed that; active diseased patients were more likely to suffered from muco-cutaneous manifestations (mouth and genital ulcerations), erythema, blackout, and active CNS events ($P<0.05$, for all), Table 2.

**Table (2): Behçet's disease symptoms frequency and disease severity**

| Variable | Total (n=36) | | Active BC (n=18) | | Inactive BC (n=18) | | P-value |
|---|---|---|---|---|---|---|---|
| **Muco- cutaneous** | | | | | | | |
| • Mouth ulceration | 18 | (50.0) | 14 | (77.8) | 4 | (22.2) | **0.001*** |
| • Genital ulceration | 14 | (38.9) | 13 | (72.2) | 1 | (5.6) | **0.000*** |
| **Cutaneous** | | | | | | | |
| • Erythema | 8 | (22.2) | 8 | (44.4) | 0 | (0.0) | **0.003*** |
| • Skin pustules | 4 | (11.1) | 4 | (22.2) | 0 | (0.0) | 0.104 |
| **Musculoskeletal** | | | | | | | |
| • Arthralgia | 18 | (50.0) | 8 | (44.4) | 10 | (55.6) | 0.505 |
| • Arthritis | 18 | (50.0) | 9 | (50.0) | 9 | (50.0) | 1 |
| **Gastrointestinal** | | | | | | | |
| • Nausea & vomiting | 2 | (5.6) | 0 | (0.0) | 2 | (11.1) | 0.486 |
| • Diarrhea | 4 | (11.1) | 2 | (11.1) | 2 | (11.1) | 1 |
| **Ocular** | | | | | | | |
| • Red eye | 14 | (38.9) | 5 | (27.8) | 9 | (50.0) | 0.171 |
| • Painful eye | 14 | (38.9) | 6 | (33.3) | 8 | (44.4) | 0.494 |
| • Blurred double vision | 4 | (11.1) | 4 | (22.2) | 0 | (0.0) | 0.104 |
| • Blackout | 12 | (33.3) | 11 | (61.1) | 1 | (5.6) | **0.000*** |
| **Neurological** | | | | | | | |
| • Headache | 15 | (41.7) | 9 | (50.0) | 6 | (33.3) | 0.310 |
| • Active CNS events | 8 | (22.2) | 7 | (38.9) | 1 | (5.6) | **0.041*** |
| • Difficult speech & hearing | 0 | (0.0) | | | | | |
| • Weakness Face, arms, and legs | 0 | (0.0) | | | | | |
| • Memory loss | 0 | (0.0) | | | | | |
| • Loss of balance | 0 | (0.0) | | | | | |
| **Pulmonary** | | | | | | | |
| • Chest pain | 4 | (11.1) | 2 | (11.1) | 2 | (11.1) | 1 |
| • Hard breathing | 4 | (11.1) | 2 | (11.1) | 2 | (11.1) | 1 |
| • Cough of blood | 2 | (5.6) | 2 | (11.1) | 0 | (0.0) | 0.486 |
| **Peripheral vascular involvement** | | | | | | | |
| • Discoloration/ swelling/ Pain/ of legs, arms or face | 2 | (5.6) | 0 | (0.0) | 2 | (11.1) | 0.486 |

Qualitative data are presented as n (%). *Significance defined by p ≤0.05.

## DISCUSSION

The purpose of our current prospective study was to examine the connection between these clinical features and disease progression in BD patients.

To the best of our knowledge, very few research have examined how clinical features and disease activity are connected in BD patients. Studies in the past have shown associated risk factors for evaluating disease activity in BD when it involves the nervous system [11], gastrointestinal affection of BD [12], and ocular symptoms of BD [13].

In the current study, we observed the median age of the studied participants was 37 years (range 20-52) years old, with high male predominance (male: female ratio was 5:1). Similarly, **Saadoun *et al.* [14], Savey *et al.* [15] and El-Najjar *et al.* [7]** reported male predominance in BD patients. It seems that the gender distribution in BD is widely affected by the ethnic origin and resident country. For example; male: female ratio was 0.63 in Korea, 0.64 in Palestine, 0.98 in Japan, 1 in Germany, 1.03 in Turkey, 1.3 in Lebanon, 1.19 in Iran, 1.42 in Greece, 1.8 in India, 2 in Morocco, 2.4 in Italy, 2.8 in Jordan, 3 in Iraq, 3.4 in Saudi Arabia, 4.9 in Kuwait, while a female predominance was seen in Britain and USA societies [3, 16-21]. In Egypt; male; female ratio was 4.8:1 [22], and 1.7:1 [7] in another Egyptian study on BD patients.

By comparing the effect of age, and gender on BD disease activity we found no significant difference between active and inactive BD patients regarding either age or sex (P>0.05). Similar finding was reported

by the recent study of **Hou and Guan** [23], also the same author stated that on univariate logistic regression analysis, age and sex were not associated with BD disease activity. However, initial studies suggested a correlation between male sex and a more severe BD illness trajectory [24]. According to data gathered from a 2-decade follow-up survey of 387 patients, male gender is a major risk factor for mortality in BD and is reported to significantly affect the expression and course of BD [8]. **Saadoun *et al.*** [14] found that male BD patients were more likely to experience a relapse than their female counterparts. At the same time, a review article that compiled data from many nations concluded that the male preponderance was not consistently validated [25].

The main causes of morbidity and mortality in BD patients are known to be ocular, neurologic, and vascular involvement, and they typically happen within the first few years of the disease's beginning [25]. In the present study, muco-cutaneous involvement (recurrent oral and genital ulcers) was the most prominent manifestations documented in 50% and 38.9% respectively and were predominant among patient with active disease status (P<0.05). In line with our study, oral aphthous ulcers were documented in 96.8% of Iranian BD patients [26]. Another Iranian study found that the oral aphthous ulceration was the commonest clinical features among BD patients documented in 90% cases, followed by genital ulcers in 60% [27]. In Kuwait oral and genital ulcers were documented in 100% and 93% respectively [28].

The prevalence of mouth and genital ulcerations in the present study was also comparable to previous Egyptian studies on BD patients where mouth and genital ulcerations were reported in 100% and 93.3% respectively [5], in 100% and 82% respectively [16], in 84.2% and 78.2% respectively [7], and in 100.0% and 35% respectively [29].

Between 30% and 70% of BD patients experience some sort of articular involvement, and for about 16.5% of those patients, this is the very first sign of the disease [30]. Joints including the knees, ankles, wrists, and elbows are especially susceptible [30, 31]. Patients with active and inactive BD had similar rates of articular involvement, as measured by the presence of arthralgia and arthritis, in the current investigation (P>0.05). Similarly, **Benamour *et al.*** [32] reported that 56.6% of BD patients suffered from articular involvement mainly knees and ankles. Another discrepancy was the prevalence of joint involvement among BD patients, which was found to be lowest in Turkey (16%), followed by 24.2 % in Korea, 34.3 % in Iran, and 57 % in Japan [33], The incidence was 54% nationwide, with the greatest rates recorded in southern China and northern Hebei province [34]. In regional countries, a higher frequency of joints involvement were documented in Kuwait (76%) [28], 48% in Iraqi [19] and 37% in Saudi Arabia [21]. In previous Egyptian studies, arthritis was documented in 30.6% [35], arthritis and arthralgia were documented in 12.5% each [6], and also **El-Najjar *et al.*** [7] reported articular involvement in 12 cases (31.6%), arthralgia in 10 (26.3%) cases and arthritis in 2 (5.3%) cases.

The prevalence of eye manifestations in our study was less than what was documented in previous studies; eye manifestations were documented in 69% in Kuwait [28], in 65% in Saudi Arabia [21], in 50.9%, in 55.6% in Iran [26], and comparable to the prevalence of eye manifestations in china which documented in 35% [35]. Studies conducted in Egypt have shown that 72.4% of the population suffers from uveitis, with 32.8% of those affected in the anterior segment, 22.4% in the posterior segment, and 17.2% in both [22], **El-Najjar *et al.*** [7] Ocular manifestations in 28 (73.7%) individuals; anterior uveitis in 51.3%; posterior uveitis in 41.3%; pan uveitis in 20.5%; decreased visual acuity in 28 BD patients (due to uveitis, retinal vasculitis, and sequelae like macular edema, cataract, and glaucoma); and blurred vision in 13.2%.

In the current study, 12 (33.3%) cases had cutaneous manifestations; 8 (22.2%) cases had erythema, and 4 (11.1%) cases had skin pustules, where erythema was more prevalent among patients with active BD status. Cutaneous manifestations were documented in 57% in Saudi Arabia 57% [21], in 75 in Iraq 75% [19], in 76% and in Kuwait [28]. A higher prevalence of cutaneous manifestations were reported in previous Egyptian studies which documented cutaneous manifestations in 53.1% [35], in 86.7% [5], and in 15.8% [7].

Neurological involvement occurs in 5-10% of BD patients in BD. It is an important manifestation of BD because associated with high morbidity and mortality. It mainly appears within 5 years from the onset of disease diagnosis [3]. In the present study, 15 (41.7%) cases suffered from headache, and 8 (22.2%) cases had active CNS events in the form of brainstem or corticospinal tract syndromes,venous sinus thrombosis,isolated behavioral symptoms,and isolated headache, which was more prevalent among patients with active BD status (P=0.041), while no cases had neurological manifestations in the form of difficult speech and hearing, weakness of face, arms, or legs, memory loss, or loss of balance.

In previous Egyptian study, neurological involvement was documented in 39.6% and headache in 30.2% [4], 12.5% of the Egyptians in another study reported experiencing headaches, and 6.3% reported experiencing hearing problems [6]. In another Egyptian study, 30% of participants reported headaches, and 10% reported hearing problems [5]. Also, another Egyptian study founded that 20% of patients had neurological damage [35], and recently **El-Najjar *et al.*** [7] reported neurological manifestations in 26%; headache and impaired cognitive functions including memory loss in

26% followed by disturbance of balance in 18%, difficulties of hearing in 16%, weakness or diminished sensation of the leg in 15.8%, weakness or diminished sensation of the arm in 8% and weakness or diminished sensation of the face in 5%.

In the present study, pulmonary manifestation was documented in 11.1% in the form of chest pain, with hard breathing; this finding was associated with coughing of blood in 2 (5.6%) cases, which may be due to involvement of pulmonary vessels. In previous Egyptian studies; pulmonary manifestation was documented in 16.7% [5], in only 6% in another study [35], in **El-Najjar *et al.*[7];** chest pain was documented in 26%, breathlessness and coughing blood in 5% for each.

The prevalence of gastrointestinal manifestations in the current study was documented in 4 (11.1%) cases who suffered from diarrhea, among two of them diarrhea was associated with nausea and vomiting. In previous Egyptian study of **Hassan *et al.*[5],** gastritis was documented in 10%, and in **El-Najjar *et al.*[7]** gastrointestinal manifestations were documented in 10.5% in the form of abdominal pain associated with nausea and vomiting.

In conclusion, the presence of muco-cutaneous, ocular manifestations, and active CNS events could reflect active disease status and poorer outcome. This finding could be helpful for earlier prediction of BD activity, especially if associated with other laboratory markers that could predict BD activity, and may help to adjust treatment accordingly. However, our study was conducted in a single center with small sample size. Our results may not be applicable for generalization. Further multi-center studies are needed to study the association of clinical manifestations with laboratory data.

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**Author contribution:** Authors contributed equally in the study.

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