Original Article

Initial Sign and Period Until the Diagnosis of Behçet's Diseased Patients in Sulaimani Rheumatology Center

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Abstract

Objective: The present study aimed to register the initial clinical findings in BD patients regarding age, sex, and family history as well as to estimate the time lapse until establishing the diagnosis.

Methods: A descriptive cross-sectional study was implemented to include 50 cases of Behçet's disease over 14 years from the Rheumatology center in Sulaimani governorate-Iraq. Data were tabulated and analyzed by chi-square and independent t-test.

Results: The sample predominates in females (56%). The male-to-female ratio was 0.78:1. Their ages ranged from 23 to 71 years (43.92 ± 12.02 years). The most affected age group was 41-50 (16 cases, 32%). To a major extent, the first reported sign was oral ulceration (94%); however, the ocular lesion was the first sign in 3 females (6%). Family history was present in relatives of 6 cases (1 male and five females). An average delay of (10.66 ± 6.77) years was noted from the initial manifestation of the first sign to the time of diagnosis.

Conclusions: Dentists could reduce the delay in Behçet's disease diagnosis because patients in clinical settings may give a history of recurrent oral ulceration with other manifestations that infer possible background of BD.

Keywords: *Behçet's disease, Oral ulceration, The initial sign.*

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Introduction

Behçet's disease (BD) is a multisystem chronic vasculitis affecting all blood vessel types and sizes, especially veins[1-3]. From the historical point of view, literature stated that Hulusi Behçet, a Turkish dermatologist, was the first to define the condition in 1937 as a triple symptom complex with aphthous stomatitis, genital ulcers, and recurrent uveitis[4]. Multiple systemic correlations of the disease, including articular, vascular, gastrointestinal, cardiac, and neurologic involvement, have become increasingly apparent during the last 65 year[5,6].

Although BD is sporadic mainly, it can occur in families. The cause is unknown. However, a mix of genetic and environmental variables may be involved. In around 60%- 56% of BD patients[7,8], the HLA-B51 genetic marker is detected. In addition, unknown environmental variables, such as microbial exposure and cellular and humoral immunity, have a pathogenic role in a vulnerable individual. The autoinflammatory-autoimmune component of BD is shown by the pro-inflammatory cytokine cascade, inflammatory responses, relapsing and remitting course, and therapeutic responses to immunosuppressive drugs[7].

Family aggregation of BD has been recorded in 1–18% of the population[9,8]. According to multi-case family studies, illness inheritance does not follow Mendelian laws[9-11]. Behçet's illness can affect anyone at any age; however, it is most common between the ages of 20 and 40[1,12]. It has a long-term course with unpredictable remissions and exacerbations[3].

The clinical signs of BD are not always the same in each patient. Although some differences in epidemiologic data between studies are attributed to regional and ethnic differences in disease manifestation, the initial manifestations, the combination of clinical symptoms, and the onset and chronologic order of each symptom vary greatly from patient to patient, even within the same ethnic group and institution. Instead, heterogeneity is one of the disease's defining characteristics. Some people have mucocutaneous symptoms, while others have severe ocular involvement, resulting in blindness[13]. A wide range of clinical presentations characterizes Behçet's illness. Recurrent mouth ulcers are the most prevalent important symptom in most cases. In Behçet's disease, however, distinguishing between recurrent aphthous stomatitis (RAS) and recurrent oral ulcers might be challenging. Patients with Behçet's illness had a higher risk of large oral ulcers (diameter greater than 10 mm) and a decreased risk of small ulcers (diameter less than 10 mm). Behçet's disease patients are more likely than RAS patients to have ulcers on two or more sites of the oral mucosa. [14] Other symptoms may take years to manifest, and mouth ulcers are seen in all patients throughout their treatment[10]. Genital ulcers also reoccur, but they are less common than mouth aphthae. They resemble oral aphthae in form and develop in the scrotum in male and the vulva in females[15]. Nongranulomatous uveitis in BD can be anterior, middle, posterior, or panuveitis, which is the most common (60 percent) in both sexes[16]. cutaneous signs of Behçet's illness include erythema nodosum (EN)-like lesions, papulopustular eruptions, small-to-medium-sized cutaneous vasculitis, and a positive pathergy test result[17]. Behçet's disease-related vascular lesions can arise in big, medium, or tiny arteries or veins[15]. Male patients were shown to have a greater rate of vascular involvement than female individuals[5,6]. Neural involvement of Behçet's disease affects 3.2–17% of patients. Some of the Neuro- Behçet's symptoms are headaches, nausea, vomiting, and visual abnormalities[6]. The most prevalent neurological complaint is migraine, comparable to migraine without brain damage[7]. The present study aimed to focus on the first site and initial sign until establishing the diagnosis of registered Behçet's disease cases and compare if there is variation in age, sex, and the presence of family history.

Patients and methods

A cross-sectional study was conducted from March to September 2021 at the Rheumatology Center of Sulaimani. It included 50 Behçet's diseased Kurdish patients diagnosed according to the international criteria[17]. Informed consent was obtained from each patient. Personal information (age, sex, address, and smoking status) and history of the disease (family history and age of diagnosis) were registered on a case sheet while carrying out each patient's interview. The details of the medical data reported by the rheumatologist were obtained from their medical files. These included; the positivity for HLA-B51 and the time between the first criteria and diagnosis. Following the recommended diagnostic criteria for BD by (ICBD), score (2) was assigned for signs and symptoms, recurrent oral ulceration, recurrent genital ulceration, and ocular lesions. However, the skin lesions, neurological and vascular manifestations, and positive Pathergy test scored one[18].

Statistical Analysis

The chi-square test was applied for nonparametric variables analyzed data, and the t-test was used to estimate the age and time differences using IBM SPSS

Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp). Statistical significant results were considered at a p-value of equal and less than 0.05.

Results

This study sample included 50 cases of Behçet's disease, 22 (44%) were male, and 28 (56%) were female. Male to female ratio was (0.78: 1); their ages ranged from 23 to 71 (mean age 43.92 ± 12.02 years), with no significant sex differences (p-value =0.14).

There were 41(82%) patients (17 males, 24 females) coming from the inside city of Sulaimani, and the remaining 9 (18%) patients (5 males and four females) came from outside the city, with no significant sex variations (p-value = 0.34).

The majority of patients were non-smokers (40, 12%). Seven males (14%) were smokers, and the other 3 (6%) were previously smokers. All the female patients had no history of smoking habits (p-value = 0.000). Family history of the disease was present in first-degree relatives of only 6 (12%) patients (1 male and five females, p-value =0.16).

Recurrent oral ulceration was the initial manifestation of the disease in 47 patients (94%). It was reported in all male patients (22, 100%) and (25, 89.3%) of female patients, yet statistically insignificant (p=0.16).

On the other hand, the ocular lesion was an initial clinical sign in 3 (6%) patients; all were females (p= 0.16).

HLAB 51 test was positive in 39 (78%) patients. An average delay of (10.66 ± 6.77) years was noted from the manifestation of the first sign to the time of diagnosis. (9.77± 6.44 in males and 11.36± 7.05 for females (p= 0.41) (Table 1).

Age-group results showed that patients were mainly affected between 41-50 (16 patients), followed by 31-40 (13 patients) age groups. However, affected females were slightly more seen in the 31-40 age groups (p = 0.86). Also, the above patients were from the inside city of Sulaimani (p= 0.93). In contrast, smoker Behcet's patients dominated the age group (20-30 years). Most patients had a negative family history regarding familial aggregation of Behçet's disease. They were mainly seen between the ages of 41-50 (15 cases), followed by the 31-40 age group (p=0.38). Furthermore, oral ulceration mainly occurred in the age group (41-50) (15 cases), and only one patient in this age group had ocular lesions (p=0.69) (Figure 1). Moreover, the shortest time between the first criteria and the diagnosis date was seen in ages 20-30 (Mean ± SD 5.57±4.11). The most prolonged period for diagnosis was in the group of patients aged between 51-60 years (15.75±7.97) p= 0.34 (Figure 2).

Table 1: Distribution of studied parameters in the total sample and both sexes.

Parameter		No.	%	Male		Female		p-value
Sex (M:F ratio= 0.78:1	Male	22	44					
	Female	28	56	No.	%	No.	%	
Address	Inside City	41	82	17	77.3	24	85.7	0.34
	Outside city	9	18	5	22	4	14.3	
Smoking habit	Smoker	7	14	7	31.8	0	100	0.000
	Non-smoker	40	12	12	54.5	28	0	
	Previous	3	6	3	13.6	0	0	
Family history	Negative	44	88	21	95.5	23	82.1	0.16
	Positive	6	12	1	4.5	5	17.9	
1st criteria	Oral	47	94	22	100	25	89.3	0.16
	Ocular	3	6	0	0	3	10.7	
HLAB51	Positive	39	78	21	95.5	18	64.3	0.029
	Negative	3	6	0	0	3	10.7	
	Not done	8	16	1	4.5	7	25	
Age	Mean ± SD	43.92±12.02		41.09±11.84		46.14±11.9		0.14
Period between 1st sign to diagnosis		10.66± 6.77		9.77±6.44		11.36±7.05		0.41

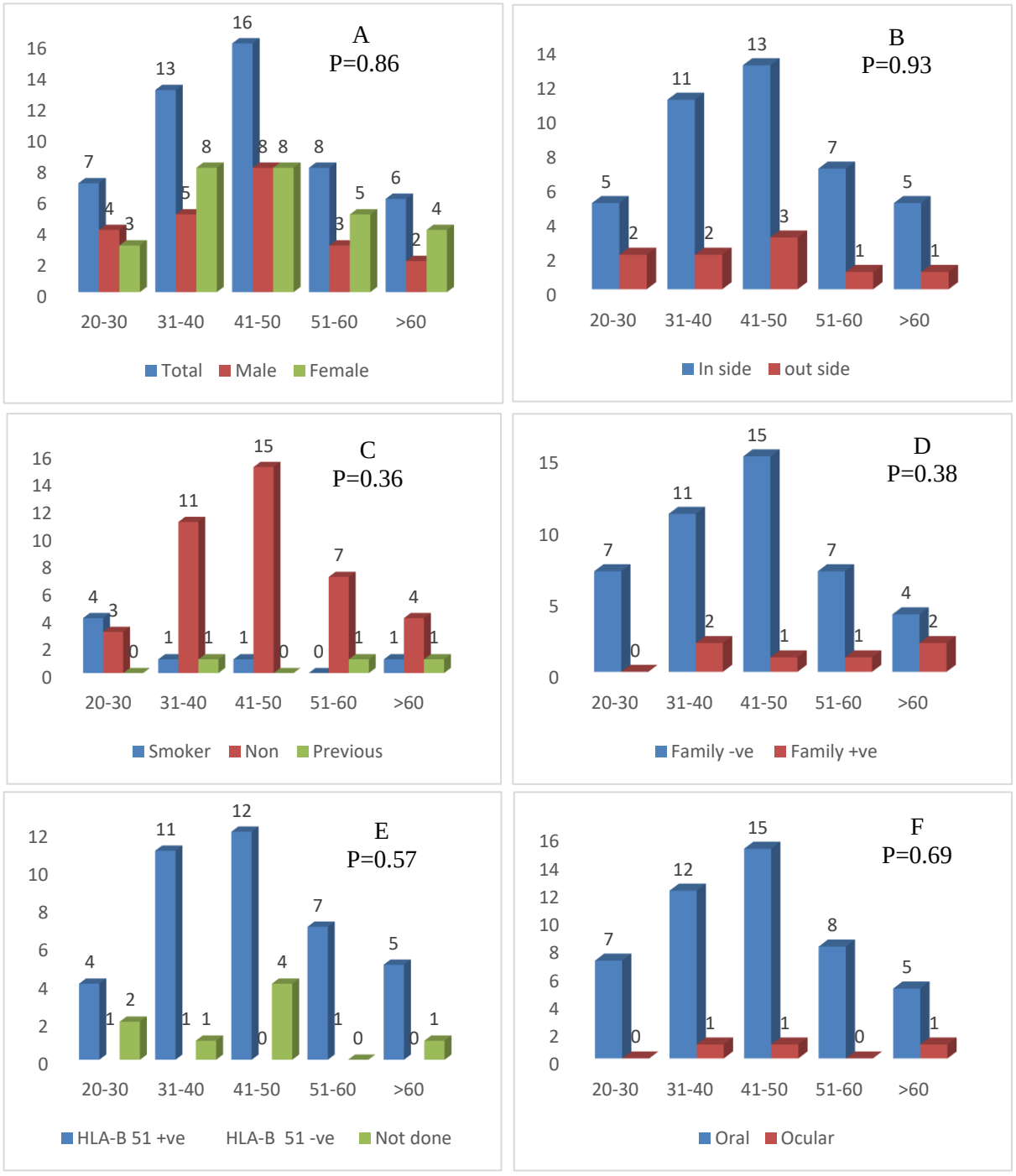

Figure 1: Frequency distribution of studied parameters according to age groups, with; A; sex, B; address, C: smoking habit, D; familial history, E; HLA-B 51 test, f; first criteria.

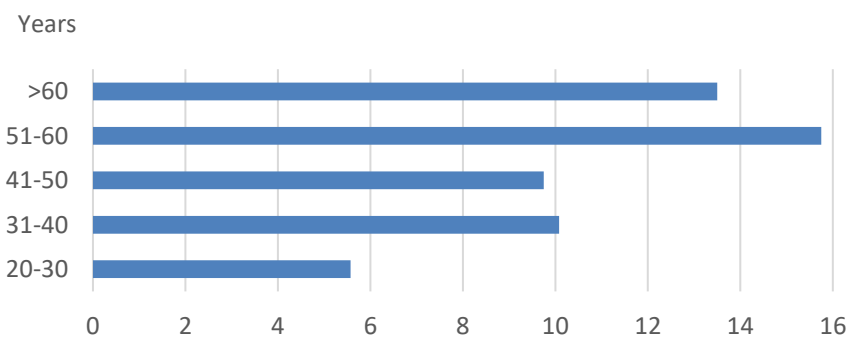

Figure 2: Mean value for the period lapse between the first sign to the time of diagnosis in different age-groups.

Discussion

Comparative studies of Behçet's disease have been performed in many countries; however, this study revealed the initial sign and period until the diagnosis. The sample included 50 Behçet's diseased patients registered in the Rheumatology center of Sulaimani city for fourteen years (2007-2021), including almost all age groups.

Concerning sex distribution of BD, the results of this study showed that women were more affected than men (56% vs. 44%). Faraj et al., in their study, included only 6 BD cases, ten incomplete BD and nine suspected BD cases. Again, females were more in diagnosed cases[8]; however, other researchers have revealed that men and women are affected by BD equally[1,13]. This discrepancy can be related to the limited sample size in the present study. The Mediterranean area has a male majority, whereas the Far East has a female preponderance[1,3]. A male predominance is observed in Arab populations, while female predominance is evident in Japan, Korea, China, the United States, and some northern European countries[7,19,20].

In our study, the male to female ratio was 0.78:1, whereas the male to female ratio was 3 in Iraq, 1.03 in Turkey, 1.19 in Iran, 2.8 in Jordan 4.9 and in Kuwait[21]. Sex variation has an impact on the clinical results as well as the severity of the condition[1]. The condition may be more severe in male patients, and vascular disease may be the leading risk factor for death in male patients, according to a long-term study conducted by Kural-Seyahi et al[22].

The age of the patients ranged from 23 to 71 years of age (mean age 43.92 ± 12.02 years). Male patients were younger (41.09±11.84) than female patients (46.14±11.9). This finding is in close agreement with that study performed in Yokohama City, Japan, where the mean age was 36.9 ± 11.9 years; male patients were younger (34.8 ± 11.1) than female patients (38.5 ±12.3)[13]; however, the study from Southeastern Turkey revealed that the mean age of cases was 32.4 ± 9.4 years. The mean ages of males and females were 34.57 ± 8.68 years and 30.8 ± 9.51 years, respectively, indicating that female patients were younger than the male patient[23].

Although familial cases have been described, no Mendelian inheritance model is specific to BD[1]. Comparable to other studies, in our study, family history was present in first-degree relatives of only 6 (12%) patients (1 male and five females, p=0.16). In a study from Turkey, Ozyurt et al. reported that BD family history was observed in (31.2%) of the studied sample[24]. HLA-B51 has been linked to BD in studies, with more than 60% of patients being positive for HLA-B51[25]. In Our study, the HLA-B 51 test was positive in 39 cases (78%), more than that reported in a previous study conducted in Sulaimani city (56%). This variation could be attributed to dissimilarity in the sample. Faraj et al. included nine suspected BD patients, ten incomplete BD patients, and six proved BD patients[8]. Several studies have confirmed a strong association of BD with HLA-B51, particularly in patients from Japan 79% (B51 and DRw52), Mediterranean, and Middle Eastern countries[26].

Concerning the first signs and symptoms of BD, our study showed that oral ulceration was the most commonly observed initial manifestation in (94%) of patients (all male patients, 100%, 89.3% of female patients). While the study conducted by Kontogiannis et al. revealed that oral ulcers are the first symptom and are a defining characteristic (97% –100 % of cases)[26].

Behçet's disease is one of the most severe causes of noninfectious uveitis and occurs in up to 50–90% of patients[27,28]. Behçet's uveitis can lead to blindness, affecting 16-25%[27]. Behçet's uveitis usually develops after 2–3 years; however, it may be an initial presentation of this systemic disease (10–20%)[28]. Our current study shows ocular lesions in (6%) of cases (all were women) as a first sign. Ocular involvement in general BD is more common in men than in women, with panuveitis being the most common symptom. Therefore, it is vital to identify BD at an earlier age, and BD screenings must be done until the end of the fifth decade[29].

Because of the diverse and often intermittent symptoms, the necessity to exclude mimics, the lack of a specific blood test and marker for the disease, and, unfortunately, a general lack of knowledge of this condition, there is sometimes a considerable time between the onset of symptoms and diagnosis of BD[7]. The mean (± SD) period between the appearance of the onset characteristic and the fulfillment of diagnostic criteria in our result was more extended than that of Alpsoy et al. (10.66± 6.77 versus 4.3±5.7 years). Similar to their findings, the duration was calculated to be longer in female patients than in males[30]. The timing of seeking a diagnosis in BD patients appears to be correlated to the severity of the condition[30], and males had a faster illness progression[30].

Conclusions

Behçet's disease has a diverse clinical course and must be early diagnosed since time is critical for effective therapy. In most cases, recurrent mouth ulcers are the most significant sign. Therefore, patients with RAS who acquire new significant or minor symptoms should be monitored for signs of Behçet's disease progression. Thus, dentists could reduce the delay in Behçet's disease diagnosis.

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