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Original Article

Predictive Factors of Severe Behçet's disease: A Longitudinal, Prospective Cohort Followed Between 1981–2020

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ABSTRACT

Introduction: Behçet's disease (BD) is a systemic vasculitis of unknown cause. The spectrum of the disease ranges from mucocutaneous manifestations to other organ diseases with relevant morbidity. Associations between disease severity and male sex, earlier age at onset, and the presence of erythema nodosum have been described.
Objectives: To evaluate clinical factors associated with manifestations of severe disease in a single-center cohort.
Methods: A longitudinal, prospective, unicentric cohort study with patients followed in a specialized outpatient clinic between 1981 and 2020. Severe BD was defined as a Krause total clinical severity score ≥4 points.
Results: We included 243 patients, of whom 31% were male, with an average follow-up time of 14.6 years. Regarding organ manifestations, all patients had mucous manifestations ($N = 243$, 100%), 133 (55%) skin, 104 (43%) joint, 71 (29%) ocular, 48 (20%) vascular, 47 (19%) neurological, 22 (9%) gastrointestinal and 1 (0.4%) cardiac involvement by BD. One hundred fifty-six (64%) patients were classified as having severe BD. Severe BD was more frequent in men ($OR = 2.004$, $p = 0.024$), increasing with age ($OR = 1.021$ per year, $p = 0.037$), in the presence of skin manifestations ($OR = 4.711$, $p < 0.001$), specifically erythema nodosum ($OR = 8.381$, $p < 0.001$), and pseudofolliculitis ($OR = 2.910$, $p < 0.001$).
In the multivariate model, variables independently associated with severe BD were male gender (*Adjusted OR* = 1.961, $p = 0.047$), erythema nodosum (*Adjusted OR* = 8.561, $p < 0.001$) and pseudofolliculitis (*Adjusted OR* = 2.372, $p = 0.007$).
Discussion: Male gender, erythema nodosum, and pseudofolliculitis were independently associated with severe BD forms and therefore should serve as warning signs to the clinician.

Factores predictivos de la enfermedad de Behçet grave: una cohorte prospectiva longitudinal seguida entre 1981-2020

Palabras clave:
Enfermedad de Behçet
Enfermedad de Adamantiades-Behçet
Vasculitis
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eritema nudoso
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RESUMEN

Introducción: La enfermedad de Behçet (EB) es una vasculitis sistémica de causa desconocida. El espectro de la enfermedad abarca desde manifestaciones mucocutáneas hasta otras enfermedades de órganos con morbilidad relevante. Se han descrito asociaciones entre la gravedad de la enfermedad y el sexo masculino, la edad de inicio más temprana y la presencia de eritema nudoso.
Objetivos: Evaluar los factores clínicos asociados con las manifestaciones de enfermedad grave en una cohorte de un solo centro.

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Métodos: Estudio de cohorte longitudinal, prospectivo y unicéntrico con pacientes seguidos en una clínica ambulatoria especializada entre 1981 y 2020. La EB grave se definió como una puntuación *Krause total clinical severity score* ≥ 4 puntos.
Resultados: Se incluyeron 243 pacientes, de los cuales el 31% eran varones, con un tiempo de seguimiento medio de 14,6 años. En cuanto a las manifestaciones orgánicas, todos los pacientes presentaron manifestaciones mucosas (n = 243, 100%), 133 (55%) piel, 104 (43%) articular, 71 (29%) ocular, 48 (20%) afectación vascular, 47 (19%) neurológica, 22 (9%) gastrointestinal y 1 (0,4%) cardiaca por EB; 156 (64%) pacientes fueron clasificados como con EB grave. La EB severa fue más frecuente en hombres (OR = 2,004, p = 0,024), aumentando con la edad (OR = 1,021 por año, p = 0,037), en presencia de manifestaciones cutáneas (OR = 4,711, p < 0,001), específicamente eritema nodosum (OR = 8,381, p < 0,001) y pseudofoliculitis (OR = 2,910, p < 0,001).
En el modelo multivariado, las variables asociadas de forma independiente con el EB grave fueron el sexo masculino (OR ajustado = 1,961, p = 0,047), eritema nudoso (OR ajustado = 8,561, p < 0,001) y pseudofoliculitis (OR ajustado = 2,372, p = 0,007).
Discusión: El sexo masculino, el eritema nudoso y la pseudofoliculitis se asociaron de forma independiente con formas graves de DB y, por lo tanto, deberían servir como signos de advertencia para el médico.

Introduction

Behçet's disease (BD) is a systemic vasculitis of unknown cause, classified among the Variable Vessel Vasculitis by the 2012 Revised International Chapel Hill Consensus Conference.[1] It was first described in 1937, by Hulusi Behçet, as a triad of recurrent oral and genital aphthosis and uveitis.[2] In addition to these classic symptoms, BD is a chronic disease, with a cumulative course, marked by periods of exacerbations and remissions, that may affect several systems such as articular, vascular, neurological, gastrointestinal, cardiac, pulmonary, or others. Therefore, the disease spectrum ranges from mucocutaneous manifestations to deep organ disease with relevant morbidity and life-threatening involvement.

Although BD has a worldwide distribution, its prevalence is higher along the ancient "silk route" extending from the Mediterranean region to the Middle East and Far East countries.[3,4] BD prevalence varies from 20–420/100,000 inhabitants in Turkey to 0.27–0.63/100,000 inhabitants in the United Kingdom.[5,6]

Organic involvement and BD's clinical course exhibit different phenotypes in different regions, although the factors that lead to these differences are not exact.[3,4,7] To date, the etiological factors of BD remains speculative. Nevertheless, infectious agents, genetic causes, immunological susceptibility factors, and fibrinolysis defects have been implicated in BD's etiopathogenesis.[8] An association of BD with the presence of HLA-B*51 allele has been reported, which was associated with greater susceptibility to the disease in the countries with the highest prevalence. However, this association does not appear in western countries.[9] HLA-B*51 positivity is not related to BD severity.[10]

The severity of BD manifestations is known to be greater in men due to an increase in morbidity related to ocular, vascular, and neurological manifestations of BD[4,10–16] and in younger patients at the onset of disease.[4,17–19] It has also been described in cohorts of patients with ocular involvement who present erythema nodosum.[11,13]

The purpose of this study was to evaluate clinical factors that are associated with the manifestations of severe BD in a single-center cohort.

Methods

Setting, patients, and study design

In our center, we carried out a prospective, longitudinal cohort study including all patients with diagnostic criteria for BD according to the International Study Group (ISG) in 1990,[20] followed as an outpatient in Clinical Immunology Unit of Centro Hospitalar e Universitário do Porto, between January-1981 and January-2020. (Centro Hospitalar e Universitário do Porto) is a tertiary-care university hospital in Porto, northern Portugal. The patients that were referred to our consultation with signs or symptoms suggestive of BD or with BD diagnosis were included in our database and the manifestations were recorded as they arose during the follow-up period. Some manifestations, namely those that were already present before admission to consultation, were registered according to the patient's information, as the onset of the first symptoms. Therefore, although the study is essentially prospective, it has a retrospective component that must be considered. On the other hand, for the purpose of this study, we included only patients with BD criteria, according to the ISG, based on the manifestations presented throughout the follow-up.

Due to the long follow-up period, it was not possible to obtain informed consent from all patients. Thus, institutional authorizations were requested to carry out this study. Hospital Ethics Committee approved the study design, and informed consent was waived [study number 2020-162(127-DEFI-129-CE)].

Data and definitions

We collected data regarding demographic features and symptoms of BD (each time of appearance of mucosae manifestations – oral aphthosis, genital aphthosis; skin manifestations – erythema nodosum, pseudofolliculitis; joint manifestations – arthralgias, monoarthritis, polyarthritis, spondyloarthritis; ocular, neurological, vascular, gastrointestinal and cardiac involvement). Ocular manifestations include uveitis, retinal vasculitis, papillitis, conjunctivitis, and scleritis. Neurological manifestations include the hemispheric, brainstem, and spinal cord syndromes, dural sinus thrombosis, and arterial occlusion of the central nervous system (CNS) vessels. Vascular manifestations include deep vein thrombosis, thrombophlebitis, arterial aneurysms, and arterial occlusion other than CNS vessels. Esophageal, gastroduodenal, intestinal, and perianal ulcers, digestive bleeding from ulcers, bowel perforation, and chronic inflammatory diarrhea were reported as gastrointestinal manifestations.

To evaluate BD severity, we used Krause's total clinical severity score (CSS) as it was the most commonly used index in previous studies.[21] This score[22] was calculated as the sum of 1 point each for mild symptoms (oral aphthosis, genital ulcers, arthralgia, and typical skin lesions such as erythema nodosum, papulopustular lesions, and folliculitis), 2 points each for moderate symptoms

(arthritis, deep vein thrombosis of the legs, anterior uveitis, and gastrointestinal involvement), and 3 points each for severe disease manifestations (posterior/panuveitis, retinal vasculitis, arterial thrombosis, neuro-Behçet's and bowel perforation). The data used for analysis comprises the cumulative manifestations that have ever occurred in a specific patient. The BD patients were categorized according to the CSS as follows: severe BD a score ≥ 4 points and mild BD a score < 4 points.[23] We have also evaluate the overall damage associated with BD according to the Behçet's Syndrome Overall Damage Index (BODI) score.[24]

The presence of HLA-B*51 allele was also collected.

The age at the beginning of the first manifestations attributed to BD, reported by the patient, was considered the age at onset, regardless of the time the diagnosis was made.

Our sample refers to a population followed in a specialized outpatient clinic, including patients referred from primary health care and other hospitals and, therefore, includes the most severe disease cases. Thus, this selection bias can mean that our sample may be underrepresented in terms of milder cases.

Statistical analysis

Categorical variables are presented as an absolute value and relative frequency, and the numerical variables as mean ± standard deviation (SD). For comparison between groups, the Pearson Chi-square test was used for categorical variables or the Fisher's exact test; the Student *t*-test was used for numerical variables.

The multivariate analysis included the variables with a statistically significant association with severe BD in the univariate analysis (defined as $p < 0.1$) and the demographic data. A multivariate, forward stepwise, logistic regression analysis was performed, defining severe BD as the dependent variable. We constructed three different models for the multivariate analysis. Each of them used age at different times, as presented along with this work (age at onset, age at diagnosis, and current age). Multivariate analysis results are expressed as odds ratios (OR) with a 95% confidence interval (95% CI) and *p*-value. The goodness of fit for all regressions was checked using the Hosmer–Lemeshow test. Statistical significance was set for *p* values < 0.05. All statistical tests were 2-sided.

Statistical analyses were performed using SPSS software (SPSS for Windows, version 24, Chicago, IL, USA).

Results

Our cohort includes 243 patients followed between 1981 and 2020, of which 75 (31%) patients are male. The current age was 49.9 (±14.3) years old (y.o.), the follow-up time was 14.6 (±8.1) years. The first signs and symptoms of the disease started at 28 (±13.3) y.o. B.D diagnosis were established when patients had, at the mean, 34.7 (±12.3) y.o. BD diagnosis was established, on average, 6.6 (±7.8) years after the onset of the first symptoms, and 0.6 (±2.2) years after admission to our consultation.

The HLA-B*51 allele was only accessed in 200 (82%) patients and present in 108 (54%). The mean Krause CSS was 5.7 (±3.5) points and a BODI score of 0.7 (±1.5) points.

Regarding organ manifestations, during the follow-up period, all patients had mucosae manifestations (*N* = 243, 100%), 133 (55%) had cutaneous, 104 (43%) joint, 71 (29%) ocular, 48 (20%) vascular, 47 (19%) neurological, 22 (9%) gastrointestinal and 1 (0.4%) cardiac involvement by BD. Manifestations by organ are detailed in Table 1.

In most patients, mucosae manifestations were the first symptoms of BD (*N* = 234, 96%). Skin involvement was present at BD onset in 29 (12%) patients. Patients exhibited signs of skin involvement seven years after the appearance of first signs of BD. Articular, ocular, vascular, gastrointestinal, and cardiac manifestations appear later in the disease course, more than nine years after the first BD signs. Table 2 presents the time elapsed between first signs of BD and each organ manifestation.

Table 1
Clinical characteristics of patients with Behçet's disease (BD).

Manifestations, by organ, *N* (%)	Total (*N* = 243)
Mucosae	243 (100%)
Oral aphthosis	243 (100%)
Genital aphthosis	181 (74.5%)
Skin	133 (54.7%)
Erythema nodosum	72 (29.6%)
Pseudofoliculitis	96 (39.5%)
Joint	104 (42.8%)
Monoarthritis	6 (2.5%)
Polyarthritis	32 (13.2%)
Spondyloarthritis	22 (9.1%)
Arthralgias	80 (32.9%)
Ocular	71 (29.2%)
Uveitis	63 (25.9%)
Retinal vasculitidis	12 (4.9%)
Papillitis	2 (0.8%)
Conjunctivitis	4 (1.6%)
Scleritis	5 (2.1%)
Amaurosis	8 (11.4%)
Vascular	48 (19.8%)
Deep vein thrombosis	28 (11.5%)
Thrombophebitis	28 (11.5%)
Arterial aneurysms	8 (3.3%)
Arterial occlusion	3 (1.2%)
Neurological	47 (19.3%)
Neuro-Behçet	36 (14.8%)
Brainstem syndrome	14 (5.8%)
Spinal cord syndrome	12 (4.9%)
Arterial occlusion CNS	5 (2.1%)
Chronic headache	20 (8.2%)
Gastrointestinal	22 (9.1%)
Esophageal ulcer	4 (1.6%)
Gastroduodenal ulcer	4 (1.6%)
Perianal ulcer	5 (2.1%)
Digestive bleeding from ulcer	4 (1.6%)
Bowel perforation	5 (2.1%)
Chronic inflammatory diarrhea	16 (6.6%)
Cardiac	1 (0.4%)

Table 2
Time elapsed between first signs of Behçet's disease (BD) and each organ involvement.

	Time elapsed between onset of BD and each organ manifestation, in years, mean (SD)
Mucosae	0.1 (0.04)
Skin	7.4 (0.74)
Joint	11.6 (0.96)
Ocular	11.0 (1.12)
Vascular	9.7 (1.32)
Neurological	14.4 (1.66)
Gastrointestinal	9.2 (1.58)
Cardiac	31 (–)

Besides BD, 22 patients presented overlap with other autoimmune diseases, namely, seven patients with Sjögren's syndrome, five with ankylosing spondylitis, two with psoriatic arthritis, two with psoriasis without joint involvement, two with antiphospholipid syndrome, one with rheumatoid arthritis, one with idiopathic thrombocytopenic purpura and another with temporal arteritis.

Severe BD

Considering Krause's CSS, 156 (64.2%) patients were classified as having severe BD. Table 3 summarizes the data regarding the comparison of subgroups with mild and severe BD. The proportion

Table 3
Demographic and clinical characteristics of patients with Behçet's disease (BD) and comparison between patients with mild and severe BD.

	Total (*N* = 243)	Mild BD (*N* = 87)	Severe BD (*N* = 156)	*p*
Male gender, N (%)	75 (30.9%)	19 (21.8%)	56 (35.9%)	**0.029**
Age (current) (years), mean (±SD)	49.9 (±14.3)	47.3 (±13.3)	51.3 (±14.2)	0.036
Age at onset (years), mean (±SD)	28.1 (±13.3)	27.7 (±14.4)	28.3 (±12.7)	0.755
Age at diagnosis (years), mean (±SD)	34.7 (±12.3)	35.3 (±13.3)	34.4 (±11.7)	0.553
Manifestations, N (%)				
Mucosae (at onset)	234 (96.3%)	86 (98.9%)	148 (94.9%)	0.163
Mucosae (cumulative)	243 (100%)	87 (100%)	156 (100%)	–
Oral aphthosis	243 (100%)	87 (100%)	156 (100%)	–
Genital aphthosis	181 (74.5%)	67 (77.0%)	114 (73.1%)	0.542
Skin (at onset)	29 (11.9%)	2 (2.3%)	27 (17.3%)	**<0.001**
Skin (cumulative)	133 (54.7%)	27 (31.0%)	106 (67.9%)	**<0.001**
Erythema nodosum	72 (29.6%)	7 (8.0%)	66 (42.3%)	**<0.001**
Pseudofolliculitis	96 (39.5%)	21 (24.1%)	75 (48.1%)	**<0.001**
Joint (at onset)	5 (2.1%)	1 (1.1%)	4 (2.6%)	0.657
Joint (cumulative)	104 (42.8%)	17 (19.5%)	87 (55.8%)	**<0.001**
Ocular (at onset)	5 (2.1%)	0	5 (3.2%)	0.163
Ocular (cumulative)	71 (29.2%)	0	71 (45.5%)	**<0.001**
Vascular (at onset)	3 (1.2%)	0	3 (1.9%)	0.555
Vascular (cumulative)	48 (19.8%)	4 (4.6%)	44 (28.9%)	**<0.001**
Neurological (at onset)	2 (0.8%)	0	2 (1.3%)	0.538
Neurological (cumulative)	47 (19.3%)	0	47 (30.1%)	**<0.001**
Gastrointestinal (at onset)	0	0	0	**–**
Gastrointestinal (cumulative)	22 (9.1%)	0	22 (14.1%)	**<0.001**
Cardiac (at onset)	0	0	0	**–**
Cardiaca (cumulative)	1 (0.4%)	0	1 (0.6%)	1.000
HLA-B*51 allele positivity, N (%)	109/200 (54.5%)	37/72 (51.4%)	72/128 (56.3%)	0.555
Krause CSS, mean (SD)	5.7 (3.5)	2.3 (0.6)	7.6 (2.9)	**<0.001**
BODI score, mean (SD)	0.7 (1.5)	0.02 (0.2)	1.0 (1.8)	**<0.001**

Statistical significance was set for p values < 0.05.

of men with severe DB was higher ($p = 0.029$). Although patients with severe BD were older (51.1 *vs.* 47.8 y.o., $p = 0.087$), we found no differences regarding age at onset of disease ($p = 0.755$) nor the age of diagnosis ($p = 0.553$).

The HLA-B*51 allele was only accessed in 128 patients with severe BD, and was present in 72 (56%) of them. We found no differences regarding the presence of HLA-B*51 allele positivity comparing mild and severe BD (51.4% *vs.*56.3%, $p = 0.555$).

In our cohort, all patients had oral aphthosis during the follow-up period, and 75% ($n = 181$) had genital ulcers. We found no differences regarding the presence of genital aphthosis between mild and severe BD patients (77% *vs.* 73%, $p = 0.542$).

On the other hand, among the 133 patients that had cutaneous manifestations, we found skin involvement more frequent in the group of patients with severe BD, both at onset and cumulative BD manifestations ($p < 0.001$), specifically erythema nodosum ($p < 0.001$) and pseudofolliculitis ($p < 0.001$) (Table 3). No significant differences were found regarding the frequency of manifestations at mucosae, joint, ocular, vascular, neurological, and gastrointestinal at BD onset. On the other hand, the presence of articular, ocular, vascular, neurological and gastrointestinal manifestations is higher in patients with severe BD, as is excepted by the Krause's CSS calculus.

No differences were found regarding the prevalence of other autoimmune diseases.

BD damage, evaluated by the BODI score, was significantly higher among patients with severe BD ($p < 0.001$). Table 4 shows the variables related to severe BD, expressed in simple OR, and the multivariate analysis results, including clinical and demographic features. In the univariate and multivariate analysis models, in addition to demographic data, we included only mucosae and skin manifestations. Using the Krause's CSS, patients who present articular, vascular, neurological and gastrointestinal manifestations will be included in a severe disease category due to the score attributed to this type of manifestations, together with the point assigned to the classical features of BD. Thus, if we included those variables in the models, we would be evaluating the same factor twice, so we chose not to include them. We constructed three different models for the multivariate analysis, in each one of them using a different age – current age, age at onset, and age at diagnosis. The results were the same in those three models; none of them returned age as an output. Variables independently associated with severe BD were male gender (*Adjusted OR* = 1.961, $p = 0.047$), erythema nodosum (*Adjusted OR* = 8.561, $p < 0.001$), and pseudofolliculitis (*Adjusted OR* = 2.372, $p = 0.007$).

Discussion

Although associations between clinical manifestations of BD and a more severe course of the disease have been described, most of these associations were described in subgroups of patients who have a specific type of organ involvement, such as ocular, intestinal, among others.[4,10–13,15–19,25] Our cohort included all patients followed at our center, regardless of specific organ involvement. This study revealed the association of the male gender as well as the presence of erythema nodosum and pseudofolliculitis, as clinical characteristics that are independently associated with manifestations of severe BD.

As for gender differences, several studies reported a higher incidence of ocular, vascular, and neurological impairment in men,[10,12,15,16] although in the latter case, the results were sometimes contradictory.[14] Using a modified form of the BD total activity index to access BD severity, Gül[10] in a cohort of 148 patients, described an increased risk of severe disease in men, in a logistic regression including demographic data, family history, and HLA-B*51 allele positivity, without including other clinical features in the analysis. Furthermore, Balta[12] described a higher incidence of ocular, neurological, and vascular manifestations in men, comparing each organic manifestation's prevalence between men and women. Likewise, Cansu[15] described a higher incidence of vascular and ocular damage in men, just as Davatchi[16] described a strong association between male sex and vascular damage. In a study that addresses BD's mortality conducted by Saadoun,[26] male sex and arterial involvement were independently associated with

Table 4
Univariate and multivariate logistic regression for clinical factors associated with severe Behçet's disease.

	Simple OR	*p*	CI 95%	Adjusted OR	*p*	CI 95%
Male gender	2.004	**0.024**	1.10–3.67	1.961	**0.047**	1.01–3.81
Age (current)	1.021	**0.037**	1.00–1.04			
Age at onset	1.003	0.754	0.98–1.02			
Age at diagnosis	0.994	0.552	0.97–1.02			
Manifestations						
Mucosae (at onset)	0.215	0.151	0.03–1.75			
Mucosae (cumulative)	–	–	–			
Oral aphthosis	–	–	–			
Genital aphthosis	0.810	0.500	0.44–1.49			
Skin (at onset)	8.895	**0.003**	2.06–38.39			
Skin (cumulative)	4.711	**<0.001**	2.68–8.29			
Erythema nodosum	8.381	**<0.001**	3.64–19.32	8.561	**<0.001**	3.65–20.11
Pseudofolliculitis	2.910	**<0.001**	1.62–5.21	2.372	**0.007**	1.62–4.46
HLA-B*51 allele positivity	1.216	0.508	0.68–2.17			

mortality. On the other hand, Bang[14] reported a higher prevalence of neurological disorders in women compared to men. Based on these studies, it is known that the disease has a more severe phenotype in men. However, the variability in the BD severity definition used in different studies makes it difficult to compare results. Our study corroborates this association, demonstrating the independent association of male gender with the most severe forms of BD in the global expression of the disease and not only limited to a subgroup of clinical manifestations.

The presence of erythema nodosum as a prognostic factor for the severe disease was only described in patients with ocular disease. Likewise, the definitions used to address BD's severity in these ocular cohorts differ. Using a worse visual prognosis as an outcome in a cohort of ocular BD, Hu[11] described a more severe BD in males presenting erythema nodosum. On the other hand, defining severe disease as death, blindness, vascular, neurological, lung, gastrointestinal and articular BD involvement, Zouboulis[13] described a more severe disease in patients presenting a triad of symptoms: ocular BD, erythema nodosum, and thrombophlebitis. Our study shows that erythema nodosum is independently associated with the most severe manifestations of BD and that this association is not limited to ocular BD cohorts.

A higher incidence of pseudofolliculitis has been more described in males than in females in several studies,[12,18,19] although others found no differences between genders.[15] The presence of pseudofolliculitis had not previously been described as a factor independently associated with severe BD manifestations. The prevalence of pseudofolliculitis is very variable in different geographical locations, with a reported prevalence of 39% from Egypt to 91% in Jordan.[7] In our population, the prevalence of pseudofolliculitis is low (39.5%) compared to other series with many patients included.[25,27,28] However, given BD's phenotypic variation in different locations, this association described in our cohort may not be reproducible in other populations. Further studies extended to other population groups are necessary to confirm it.

In our study, the increase of the current age is associated with severe BD, with the odds for severe BD increasing 2% per year, without considering interaction with other factors. This finding is in accordance with the disease's progressive course and the appearance of organ manifestations over the years. However, when age was analyzed together with other factors, we found no association between severe BD and the patient's age. The onset of BD clinical manifestations is around the third decade of life in most studies,[7] the same in our population, 28.1 years. We did not find any association between the age of onset of symptoms and severe BD. Studies that reported this association analyzed the effect of age without considering interaction with other factors[18,19] or considered only a group of patients with a specific organ target.[17,29,30] Yazici[18] demonstrated that men with the onset of symptoms before 24 y.o. had more eye disease. Alpsoy[19] showed that patients with age at onset under 40 y.o. had more ocular involvement and genital ulcers. In patients with intestinal BD, Jung[17] reported that age at onset, greater severity of the intestinal disease, and the prevalence of volcano-shaped ulcers are associated with a worse prognosis. Also, in patients with intestinal BD, Zhang[30] associated the earlier age at onset with shorter event-free survival. Similarly, in a cohort with ocular BD, Belkhadir[29] describes a worse ocular outcome in patients with earlier age at onset and with a higher number of recurrences. The authors raise the hypothesis that this association with age may be due to greater exposure to BD flares throughout life, with periods of exacerbation and cumulative damage and not precisely more severe manifestations when they appear at an earlier age, however, this study does not allow us to draw these connections.

As in previous studies, there was no association between the HLA-B*51 allele's positivity and the presence of severe BD.[10]

Regarding the sequence of manifestations' appearance, in most patients of our cohort, mucosae manifestations were the first to appear, followed by skin involvement, around seven years later. Other organ manifestations arose almost a decade later. Thus, we believe that these clinical characteristics can assist the clinician in the follow-up of these patients and serve as a warning sign for earlier detection and timely treatment and prevention of deep organ damage. It is important to notice in these time interval's analysis, that the real differences may not be that big. On the one hand, both mucosal and cutaneous manifestations are detectable without the use of complementary exams and, therefore, they can either be either noticed by the patient or be observed by the clinic, and thus, be detected practically at the onset time. On the other hand, usually deep organ involvement diagnosis requires complementary tests and, therefore, can be detected later. Over the past few years, technological developments in terms of complementary tests have increased the detection of BD's deep organ manifestations, namely vascular and neurological involvement, among others. In our study, due to the long follow-up period, these manifestations, especially for the patients included within the first years, may be underrepresented, although the long inclusion period together with the cumulative BD manifestations presented, tends to lessen this problem.

BD diagnosis relies basically on the identification of several clinical characteristics, that can emerge separated by several years, enough to fulfill the classification criteria (with a specificity above 95% [31]).[32,33] This can represent underdiagnosis in the initial stages and accounts for the lag time between the BD onset and diagnosis, on average, 7 years in our study. Furthermore, some BD phenotypes can mimic other autoinflammatory diseases, especially the antineutrophil cytoplasmatic antibodies (ANCA)-associated vasculitis (AAV).[34] The distinction between these entities can be a challenge, due to manifestations overlap. ANCA positivity does not

always help in the diagnosis: there are ANCA-negative AAV, and, on the other hand, ANCA has been detected in a wide range of diseases, other than AAV[35], including BD with vascular involvement.[34] To date, no known biomarker has been reported for BDś, but efforts have been made.32 Both factors can introduce a diagnostic bias in our study, underrepresenting BD cases at an earlier stage and, also, patients with atypical presentations. The authors believe that, in the future, the identification of such biomarkers can help to distinguish these diseases, and possibly allow an earlier diagnosis.

Our study's main strengths lie in the fact that we have considered the multiorgan manifestations of BD and were not limited to a specific organ, in the high number of patients followed in our center, and in the long follow-up period. The main weaknesses of this study are due to its observational nature with its inherent limitations as well as to the fact that we used a definition for severe BD a score with a final result that can translate just one or an association of organs, which can hide whether these associations are due to a preferential organ achievement. In our opinion, our study raises future questions, namely whether these associations vary with gender or with the involvement of a specific organ.

Conclusions

Male gender, erythema nodosum, and pseudofolliculitis were associated with severe DB. Mucous manifestations are usually the first sign of the disease and, together with skin involvement, usually, appear before other organs are affected. Thus, these manifestations can help as an alert for the clinician, indicating that the patient who presents them may develop severe BD manifestations in the future.

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Conflict of interest

None.

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References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11.
2. Behçet H. Uber rezidivierende, apthöse durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. Dermatol Wochenschr. 1937;36:1152–7.
3. Alpsoy E. Behcet's disease: a comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. J Dermatol. 2016;43:620–32.
4. Akkoc N. Update on the epidemiology, risk factors and disease outcomes of Behcet's disease. Best Pract Res Clin Rheumatol. 2018;32:261–70.
5. Yurdakul S, Yazici H. Behcet's syndrome. Best Pract Res Clin Rheumatol. 2008;22:793–809.
6. Yazici Y, Yurdakul S, Yazici H. Behcet's syndrome. Curr Rheumatol Rep. 2010;12:429–35.
7. Davatchi F, Chams-Davatchi C, Shams H, Shahram F, Nadji A, Akhlaghi M, et al. Behcet's disease: epidemiology, clinical manifestations, and diagnosis. Expert Rev Clin Immunol. 2017;13:57–65.
8. Evereklioglu C. Current concepts in the etiology and treatment of Behcet disease. Surv Ophthalmol. 2005;50:297–350.
9. Al-Mutawa SA, Hegab SM. Behcet's disease. Clin Exp Med. 2004;4:103–31.
10. Gul A, Uyar FA, Inanc M, Ocal L, Tugal-Tutkun I, Aral O, et al. Lack of association of HLA-B*51 with a severe disease course in Behcet's disease. Rheumatology (Oxford). 2001;40:668–72.
11. Hu K, Lei B, Kijlstra A, Li P, Zhang X, Xiao X, et al. Male sex, erythema nodosum, and electroretinography as predictors of visual prognosis after cataract surgery in patients with Behcet disease. J Cataract Refract Surg. 2012;38:1382–8.
12. Balta I, Akbay G, Kalkan G, Eksioglu M. Demographic and clinical features of 521 Turkish patients with Behcet's disease. Int J Dermatol. 2014;53:564–9.
13. Zouboulis CC, Turnbull JR, Martus P. Univariate and multivariate analyses comparing demographic, genetic, clinical, and serological risk factors for severe Adamantiades–Behcet's disease. Adv Exp Med Biol. 2003;528:123–6.
14. Bang D, Oh S, Lee KH, Lee ES, Lee S. Influence of sex on patients with Behcet's disease in Korea. Adv Exp Med Biol. 2003;528:59–63.
15. Cansu DU, Kasifoglu T, Korkmaz C. Do clinical findings of Behcet's disease vary by gender?: a single-center experience from 329 patients. Eur J Rheumatol. 2016;3:157–60.
16. Davatchi F, Shahram F, Chams-Davatchi C, Sadeghi Abdollahi B, Shams H, Nadji A, et al. Behcet's disease: is there a gender influence on clinical manifestations? Int J Rheum Dis. 2012;15:306–14.
17. Jung YS, Yoon JY, Hong SP, Kim TI, Kim WH, Cheon JH. Influence of age at diagnosis and sex on clinical course and long-term prognosis of intestinal Behcet's disease. Inflamm Bowel Dis. 2012;18:1064–71.
18. Yazici H, Tuzun Y, Pazarli H, Yurdakul S, Ozyazgan Y, Ozdogan H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behcet's syndrome. Ann Rheum Dis. 1984;43:783–9.
19. Alpsoy E, Donmez L, Onder M, Gunasti S, Usta A, Karincaoglu Y, et al. Clinical features and natural course of Behcet's disease in 661 cases: a multicentre study. Br J Dermatol. 2007;157:901–6.
20. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990;335:1078–80.
21. Hatemi G, Merkel PA, Hamuryudan V, Boers M, Direskeneli H, Aydin SZ, et al. Outcome measures used in clinical trials for Behcet syndrome: a systematic review. J Rheumatol. 2014;41:599–612.
22. Krause I, Rosen Y, Kaplan I, Milo G, Guedj D, Molad Y, et al. Recurrent aphthous stomatitis in Behcet's disease: clinical features and correlation with systemic disease expression and severity. J Oral Pathol Med. 1999;28:193–6.
23. Aksu K, Kitapcioglu G, Keser G, Berdeli A, Karabulut G, Kobak S, et al. Fcgamma RIIa, IIIa and IIIb gene polymorphisms in Behcet's disease: do they have any clinical implications? Clin Exp Rheumatol. 2008;26:S77–83.
24. Piga M, Floris A, Espinosa G, Serpa Pinto L, Kougkas N, Lo Monaco A, et al. Development and preliminary validation of the Behcet's syndrome Overall Damage Index (BODI). RMD Open. 2020:6.
25. Bang D, Lee JH, Lee ES, Lee S, Choi JS, Kim YK, et al. Epidemiologic and clinical survey of Behcet's disease in Korea: the first multicenter study. J Korean Med Sci. 2001;16:615–8.
26. Saadoun D, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M, et al. Mortality in Behcet's disease. Arthritis Rheum. 2010;62:2806–12.
27. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al. Behcet's disease in Iran: analysis of 6500 cases. Int J Rheum Dis. 2010;13:367–73.
28. Kim DY, Choi MJ, Cho S, Kim DW, Bang D. Changing clinical expression of Behcet disease in Korea during three decades (1983–2012): chronological analysis of 3674 hospital-based patients. Br J Dermatol. 2014;170:458–61.
29. Belkhadir K, Boutimzine N, Laghmari M, Amazouzi A, Tachfouti S, Cherkaoui O. [Prognostic factors of ocular involvement in Behcet's disease]. J Fr Ophtalmol. 2019;42:612–7.
30. Zhang L, Tian Y, Ye JF, Lin CH, Guan JL. Poor prognostic factors in patients with newly diagnosed intestinal Adamantiades–Behcet's disease in the Shanghai Adamantiades–Behcet's disease database: a prospective cohort study. Orphanet J Rare Dis. 2019;14:274.
31. Davatchi F, Sadeghi Abdollahi B, Chams-Davatchi C, Shahram F, Shams H, Nadji A, et al. The saga of diagnostic/classification criteria in Behcet's disease. Int J Rheum Dis. 2015;18:594–605.
32. Hu CJ, Pan JB, Song G, Wen XT, Wu ZY, Chen S, et al. Identification of Novel Biomarkers for Behcet Disease Diagnosis Using Human Proteome Microarray Approach. Mol Cell Proteomics. 2017;16:147–56.
33. Leonardo NM, McNeil J. Behcet's Disease: Is There Geographical Variation? A Review Far from the Silk Road. Int J Rheumatol. 2015;2015:945262.
34. Kim MK, Kwon HC, Song JJ, Park YB, Lee SW. Antineutrophil Cytoplasmic Antibody Positivity Is Associated with Vascular Involvement in Behcet's Disease. Yonsei Med J. 2021;62:149–58.
35. Csernok E. The Diagnostic and Clinical Utility of Autoantibodies in Systemic Vasculitis. Antibodies (Basel) 2019; 8.