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Original Article

Behçet's Disease: The Clinical and Demographic Characteristics of 406 Patients

Behçet Hastalığı: 406 Hastanın Klinik ve Demografik Özellikleri

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Objectives: In this study, we aim to describe and investigate the demographic and clinical features, prognostic factors, ocular, and systemic manifestations of the patients with Behçet's Disease.

Patients and methods: The study included 406 patients (306 males, 100 females; 36.1 years; range 12 to 76 years) who met the classification criteria of the International Study Group for Behçet's Disease. The clinical and demographic characteristics including age at onset, sex, type of ocular involvement, visual acuity, systemic manifestations, and initial signs, and treatment modalities were reviewed.

Results: The mean age at onset was 27.6±7.2 years in male patients and 29.0±9.3 years in females. There were no significant differences between both sex in terms of the frequency of ocular involvement (68.9% in male, 65.0% in female, p=0.163) and bilaterality of the ocular involvement (56.2% in male and 53.0% in female, p=0.67). The most common initial presenting manifestation of the disease was oral aphthous ulcer which was seen in 71.9% of the patients, followed by ocular involvement (23.4%). The leading clinical features were oral aphthous ulcers (100%), followed by genital ulcers (82.8%) and ocular manifestations (80.3%). HLA-B51 was positive in 170 of 372 patients (45.7%). HLA-B51 positivity had no effect on the frequency and severity of the ocular inflammatory episodes. Of 306 males, 141 (46.1%) and of 100 females 29 (29.0%) had severe ocular episodes, while 34.6% (n=106) of males and 21% (n=21) of females had frequent ocular involvement. Males had more frequent (p=0.03) and more serious (p=0.015) ocular inflammatory episodes than females. Cyclosporine A was the most commonly preferred agent for patients with frequent episodes (24.3%; p=0.019).

Conclusion: Ocular involvement in Behçet's disease is significantly more frequent and severe in men. The main prognostic criteria affecting the visual acuity are the severity and frequency of ocular involvement.

Key words: Behçet disease; HLA-B51; inflammatory episodes; uveitis; visual prognosis.

Amaç: Bu çalışmada Behçet hastalığı olan kişilerde hastalığın demografik ve klinik özellikleri, prognostik faktörleri, oküler ve sistemik bulgularının tanımlanması ve araştırılması amaçlandı.

Hastalar ve yöntemler: Çalışmaya Uluslararası Behçet Hastalığı Çalışma Grubu'nun sınıflama kriterlerini karşılayan 406 hasta (306 erkek, 100 kadın; ort. yaş 36.1; dağılım 12-76) dahil edildi. Başlangıç yaşı, cinsiyet, oküler tutulum tipi, görme keskinliği, sistemik bulgular ve başlangıç bulguları dahil olmak üzere klinik ve demografik özellikler ve tedavi yöntemleri gözden geçirildi.

Bulgular: Ortalama başlangıç yaşı erkeklerde 27.6±7.2 yıl, kadınlarda ise 29.0±9.3 yıl idi. Oküler tutulum sıklığı (erkeklerde %68.9, kadınlarda %65; p=0.163) ve her iki gözde tutulum sıklığı (erkeklerde %56.2, kadınlarda %53.0; p=0.67) açısından, her iki cinsiyet arasında anlamlı fark yoktu. Hastalığın en sık görülen ilk başlangıç bulgusu %71.9 ile oral aftöz ülser iken, bunu %23.4 ile oküler tutulum izliyordu. Başlıca klinik bulgu oral aftöz ülser iken (%100), bunu genital ülser (%82.8) ve oküler tutulum (%80.3) izliyordu. HLA-B51, 372 hastanın 170'inde pozitifti (%45.7). HLA-B51 pozitifliğinin oküler inflamatuvar atakların sıklığı ve ciddiyeti üzerinde bir etkisi yoktu. Üç yüz altı erkeğin 141'inde (%46.1) ve 100 kadının 29'unda (%29.0) ağır oküler atak mevcut olup, erkeklerin %34.6'sında (n=106) ve kadınların %21'inde (n=21) sık oküler tutulum izlendi. Erkeklerdeki ataklar, kadınlarınkine göre daha sık (p=0.03) ve daha ağırdı (p=0.015). Siklosporin A, sık atak geçirenlerde en sık tercih edilen ilaçtı (%24.3; p=0.019).

Sonuç: Behçet hastalığında oküler tutulum erkeklerde anlamlı olarak daha sık ve ağır seyreder. Görme keskinliğini etkileyen başlıca prognostik kriter, oküler tutulumun sıklığı ve şiddetidir.

Anahtar sözcükler: Behçet hastalığı; HLA-B51; inflamatuvar atak; üveit; görme prognozu.

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Behçet's disease is a multisystemic disease with occlusive vasculitis of unidentified origin. Today the criteria used the most to diagnose Behçet's disease are the same ones which were determined by the International Study Group for Behçet's Disease in 1990.[1] Diagnosis is often difficult, especially during the early stages of the disease.

The major symptoms are oral aphthous ulcers, genital ulcerations, skin lesions, and ocular manifestations. Ocular involvement is frequent and is mainly seen as posterior or panuveitis.

There are various systemic manifestations of the disease including skeletal system involvement such as arthritis, sacroiliitis, and spondyloarthropathy along with gastrointestinal, neurological, and vascular involvement. Even rare manifestations such as pericarditis, myocardial infarctions, epididymitis, and glomerulonephritis are possible. Life expectancy is shorter in young males than in females because of the tendency to have a more severe course of the disease in males.[2] There are many treatment options available including systemic steroids, immunosuppressives, immunomodulatory drugs, and biological agents such as tumor necrosis factor-alpha (TNF-α) inhibitors and interferon-alpha (INF-α).

In the present study, the aim was to describe and investigate the demographic and clinical features, prognostic factors, ocular and systemic manifestations, regional characteristics, and treatment options of patients with Behçet's disease living in the Çukurova region, which is located in the southern part of Turkey.

PATIENTS AND METHODS

Four hundred and six consecutive patients (306 males, 100 females; 36.1 years; range 12 to 76 years) were enrolled in the study, which was conducted with patients who met the classification criteria of the International Study Group for Behçet's Disease, who had been followed up primarily by the Çukurova University Ophthalmology Department Uvea-Behçet Service, or who had been referred by the Rheumatology Department between 1995 and 2010. Therefore, the presence of ocular involvement was not the only inclusion criteria. All patients who had been diagnosed with Behçet's disease and who had been examined by the ophthalmology department were included. Demographic data including age, age at onset, gender, ocular findings including laterality, and the presence and type of uveitis along with visual acuity, systemic manifestations, and treatment modalities was collected from the medical records of the patients. Changes in visual acuity were assessed as an increase, decrease, or no change during follow-up only for those for whom eyes were involved. A rise in visual acuity was defined as an increase of one or more lines from initial visual acuity while a decline in visual acuity was defined as a decrease of one or more lines from initial visual acuity using the Snellen chart.

The initial manifestation of the disease leading to the diagnosis, and the ocular and extraocular manifestations at certain points in time were recorded. An ocular inflammatory episode was defined as an acute intraocular inflammation observed by slit-lamp microscopy or funduscopy. Patients who had only iridocyclitis, either with or without hypopyon, were classified as having anterior uveitis. Patients who had vitritis with retinitis and/or vasculitis were classified as having posterior uveitis, and those who had anterior and posterior uveitis at the same time were classified as having panuveitis.

A severe ocular inflammatory episode was defined as an acute episode with vitritis, retinitis, and vasculitis. Frequent attacks were defined as having more than three attacks per year.

Approval was obtained from the institutional review board before collection of the medical records.

All data was assessed using the Statistical Package for the Social Sciences (SPSS) software package version 14.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were used for determining the distribution of the age, age at onset, sex, extraocular clinical manifestations, initial manifestations, type of ocular involvement, and treatment modalities. A chi-square test and Fisher's exact test were used for the categorical variables. A p value of less than 0.05 was considered significant.

RESULTS

The male/female ratio was 3.1/1. The mean age at onset of the disease was 27.6±7.2 (range 11-48) years for males and 29.0±9.3 (range 14-71) years for females (p=0.139). The mean follow-up time was 5.1±4.6 years (range 1-15).

The most common extraocular clinical manifestation was oral ulcers (100%). The distribution of the extraocular manifestations of the disease during follow-up in both sexes is demonstrated in Table 1.

The most frequent initial manifestation was oral aphthous ulcers (71.9%) followed by ocular involvement (23.4%) (Table 2).

Table 1. Extraocular clinical manifestations in 406 patients with Behçet's disease during follow-up

Type of manifestation	Patients						
	Total (n=406)		Male (n=306)		Female (n=100)		
	n	%	n	%	n	%	*p*
Oral ulcers	406	100.0	306	100.0	100	100.0	–
Genital ulcerations	336	82.8	254	83.0	82	82.0	0.879
Skin lesions	113	27.8	86	28.1	27	27.0	0.898
Trombophlebitis	35	8.6	30	9.8	5	5.0	0.156
Neurological involvement	22	5.4	20	6.5	2	2.0	0.124

Table 2. Type of initial manifestation in the 406 patients with Behçet's disease

Initial manifestation	Patients						
	Total (n=406)		Male (n=306)		Female (n=100)		
	n	%	n	%	n	%	*p*
Oral ulcers	292	71.9	217	70.9	75	75.0	
Ocular involvement	95	23.4	73	23.9	22	22.0	
Genital ulcerations	7	1.7	5	1.6	2	2.0	
Arthritis	5	1.2	4	1.3	1	1.0	0.737
Skin lesions	4	0.9	4	1.3	0	0	
Neurological symptoms	1	0.2	1	0.3	0	0	
Trombophlebitis	2	0.5	2	0.7	0	0	

Ocular involvement was observed in 80.3% (n=326) of the patients, and it was bilateral in 56.2% (n=172) of men, and 53.0% (n=53) of women (p=0.677). There was no statistically significant difference in ocular involvement, anterior segment involvement, presence of hypopyon, presence of vitritis, or optic nerve head involvement between males and females. However, vasculitis and retinitis were seen more frequently in men than in women (p=0.001 and p=0.001, respectively). The ocular findings and type of uveitis according to gender are shown in Table 3 and Table 4.

An assessment for human leukocyte antigen B51 (HLA-B51) positivity was performed in only 372 patients. Positive results were found in 170 of 372 patients (45.7%), with 47.7% being males (134/281) and 39.6% being females (36/91). The frequency of HLA-B51 positivity was similar for both sexes (p=0.189), and it had no effect on the severity and frequency of the inflammatory episodes (p=0.06 and p=0.412).

Severe ocular episodes occurred in 141 out of 306 males (46.1%) and 39 out of 100 females. Twenty-nine (29.0%) had severe ocular episodes, and 106 of the males (34.6%) and 21 of the females (21%) had frequent ocular involvement. The frequency and severity of ocular inflammatory episodes were significantly higher in men compared with women (p=0.03; p=0.01, respectively) (Table 5).

Table 3. Ocular findings observed during the follow-up of 406 patients with Behçet's disease and distribution of the findings between genders

Clinical finding	Involved eyes						
	Total (n=406)		Male (n=306)		Female (n=100)		
	n	%	n	%	n	%	*p*
Anterior uveitis*	183	45.1	132	43.1	51	51.0	0.138
Hypopyon	35	8.6	27	8.8	8	8.0	0.643
Vitritis	164	40.4	126	41.2	38	38.0	0.275
Retinitis	114	28.1	97	46.4	17	20.5	0.001
Vasculitis	111	27.3	93	30.4	18	18.0	0.001
Papillitis	83	20.4	68	22.2	15	15.0	0.07

* Isolated or a part of panuveitis.

Table 4. Type of uveitis during the follow-up of the 406 patients and comparisons between genders

Type of uveitis	Total (n=406)		Male (n=306)		Female (n=100)		
	n	%	n	%	n	%	*p*
Anterior uveitis*	40	9.9	26	8.5	14	14	0.12
Posterior uveitis	231	56.9	181	59.2	50	50	0.13
Panuveitis	140	34.5	103	34	37	37	0.55

* Isolated anterior uveitis.

Systemic corticosteroids were mainly used during acute inflammatory episodes and were tapered during remission since systemic immunosupressives or immunomodulatory drugs were preferred for maintenance therapy. Cyclosporin A was found to be the most preferred agent for patients having more frequent ocular inflammatory episodes (24.3%) (p=0.019).

The changes in visual acuity are described in Table 6. The number of male patients who had a decrease in visual acuity during follow-up was higher compared with the number of females; however, there was no statistical difference in visual acuity changes between genders.

The factors which could affect the final visual acuity were analyzed by using multivariate logistic regression analysis. The results showed that the most significant factors were the frequency (p=0.006) and severity (p=0.004) of the inflammatory episodes. The age at onset (p=0.221), gender (p=0.835), HLA-B51 positivity (p=0.95), and presence of neurological involvement (p=0.190) were found to have no statistically significant effect on the final vision according to the regression analysis.

DISCUSSION

Behçet's disease has well defined endemic preferences. Regional differences in clinical characteristics may exist between populations. The highest incidence is seen along the ancient Silk Road from the Mediterranean countries to the Middle East, particularly between 30° and 45° latitude north, and in Turkey.[3-5] The prevalence of Behçet's disease is 8-37/10.000 in Turkey.[6] Gül et al.[7] calculated in their familial aggregation study a sibling recurrence risk ratio, defined as the ratio of the risk of being affected among the siblings of the patients or the risk of being affected in the general population, of between 11.4 and 52.5. This supports the fact that a deep genetic background for the disease is present. Our hospital is the tertiary referral center in southern Turkey. Many people with different genetic properties currently live in this area, and their medical records may help improve the understanding of the course of the disease in one of the endemic areas in Turkey.

Table 5. Frequency and severity of inflammatory episodes between genders

Characteristics of episodes	Male (n=306)		Female (n=100)		
	n	%	n	%	*p*
Frequency					
Rare	200	65.4	79	79.0	0.03
Frequent	106	34.6	21	21.0	
Severity					
Mild	165	54.0	71	71.0	0.01
Severe	141	46.1	29	29.0	

Table 6. Changes in visual acuity of the involved eyes during follow-up between genders

Type of manifestation	Visual acuity changes								
	Decrease		Increase		No change		*Total*		
	n	%	n	%	n	%	n	%	*p*
Males	46	21	39	17.8	134	61.2	219	71.6	0.453
Females	10	14.9	10	14.9	47	70.2	67	67.0	

The male-to-female ratio calculated in the present study was higher than found in other large cohorts.[8,9] This difference could be the result of the referral pattern of the neighboring regions. Patients with more severe and frequent episodes (mostly males) were referred more often, so our findings may represent the worst spectrum of the disease.

The frequency of extraocular manifestations was similar to that found in other literature. The most common presentation of the disease in our study was oral aphthous ulcerations, and this is in concordance with most other studies from Turkey, Europe, and the United States. However, it was higher than the rate of 39.7% found in Egypt.[10-14] Tugal-Tutkun et al.[11] showed in their large observational case series that the rate of genital ulcers was 59.8%. This is lower than the rate found in our present study (82.8%), which might reflect the heterogenity of the population living in the Çukurova region since this part of Turkey has distinct ethnic properties compared with other regions.

The disease was found to be strongly associated with the major histocompatibility complex antigen HLA-B51 in the literature,[5] but whether HLA-B51 positivity is correlated with the prognosis of the disease is still a matter of discussion.[15,16] In the present study, no significant association between HLA-B51 positivity and severity or frequency of the inflammatory episodes was demonstrated, which contrasts with our previous study.[17] This could be the result of the higher number of patients who were tested for HLA-B51 in this study. Other genetic and/or environmental factors seem to be more important than HLA-B51 when examining the severity and progression of Behçet's disease.[15] The ocular involvement rate (80.3%) was higher compared with earlier reports.[10,18] Ocular manifestations as initial symptoms were reported in 10-20% of the patients.[19] This rate was similar to the one found in this study (23.4%). Our study population was composed of completely of patients with Behçet's disease who were admitted directly or referred to our clinic regardless of their ocular involvement status. This may explain the lower frequency of ocular manifestation as an initial presentation of the disease. The ocular disease most commonly associated with Behçet's is recurrent nongranulomatous uveitis with necrotizing obliterative vasculitis. This affects the anterior or posterior segment of the eye or both. Unilateral involvement presents usually with anterior uveitis, but bilateral panuveitis with a chronic relapsing course is seen in 75% of patients. Posterior involvement is more serious.[20] The main finding of the anterior disease in the past was anterior uveitis with hypopyon,[21] but this is very rare today due to early diagnosis and proper treatment. In the present study, the rate of hypopyon was 7.4% at initial presentation. The most common type of ocular involvement was posterior uveitis (56.9%). This rate was higher than what was found in other literature.[11,22-24] In our study, it was shown that women have a more favorable prognosis than men. This could be related to the higher frequency and preponderance of severe inflammation (retinitis and vasculitis) in men. Males had more frequent ($p=0.03$) and more serious ($p=0.01$) ocular involvement than females. Men had a significantly higher number of inflammatory episodes with vasculitis and/or retinitis. This is in concordance with the findings of the study by Tugal-Tutkun et al.[11] which showed that the ocular attacks with hypopyon, vitritis, vasculitis, and papillitis were significantly more frequent in men in Turkey. We found that the most preferred systemic treatment was systemic corticosteroids alone or in combination with immunosuppressive or immunomodulatory drugs. Kump et al.[25] demonstrated in their large series that systemic corticosteroid treatment was used in 96% of patients in the 1960s and 84% in the 1990s. The use of steroids, especially as monotherapy, fell significantly from 1960 to 2000. This supports the fact that there is an inevitable predilection toward using corticosteroid sparing agents, especially azathioprine and cyclosporine A[11,25-27] because of the various side effects associated with steroids. As a result, we can conclude that in Behçet's disease, the main prognostic factors affecting the visual acuity were severity and frequency of the inflammatory episodes.

The present study has several potential limitations that are common to most retrospective studies. There is the possibility of selection bias. It must be remembered that all patients with Behçet's disease were enrolled in the study whether an ocular manifestation was present or not. The population studied may not be homogeneous because it mainly consisted of patients who were referred from various clinics and because the Çukurova region is a heterogeneous community with large amounts of migration. This can result in immigration bias. There are many people living there from different ethnic groups who are members of socially, racially, and economically diverse populations.

The results of the study are comparable to those found in the previous literature and can not be generalized to

apply to all patients with Behçet's disease. However, the results provide beneficial information that can be added to the literature concerning the regional characteristics of the disease in southern Turkey.

Declaration of conflicting interests

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