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Does Familial Occurrence or Family History of Recurrent Oral Ulcers Influence Clinical Characteristics of Behçet's Disease?

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SUMMARY Recently, family history and increased frequency of some isolated manifestations of the disease in relatives of patients have been thought to play an important role in the etiopathogenesis of Behçet's disease (BD). Family history has been proposed to participate in diagnostic criteria. Investigating features of patients with different family histories may give an additional insight in understandings BD. The aim of this study was to explore the effect of familial occurrence and family history of recurrent oral ulcers (ROUs) on the clinical features of BD. We analyzed retrospectively 141 BD patients according to the International Study Group criteria. Family history of BD was present in 31.2%, family history of ROUs without BD in 31.9%, and negative family history for BD and ROUs in 36.9% of study patients. All patients were evaluated with respect to demographic and clinical features. There was no significant difference in most clinical features among patients with different family histories ($p>0.05$). Besides, patients with family history of BD and/or ROUs had longer duration of ROUs before diagnosis and more frequent extragenital ulcers than patients with negative family history of BD and ROUs ($p<0.05$ and $p<0.01$, respectively). These findings did not show any strong effect of familial occurrence or positive family history of ROUs on all clinical characteristics of BD. However, sporadic ROUs should be considered an early predictor of probable BD in patients with family history of BD and/or ROUs, and they should be followed up carefully. Further studies including genetic testing of patients and their relatives are needed.

KEY WORDS: familial Behçet's disease, family history of recurrent oral ulcers

INTRODUCTION

Behçet's disease (BD) is a multisystem disorder of unknown origin characterized by recurrent oral ulcers (ROUs), mucocutaneous disorders and ocular findings. Also, BD may affect central nervous system, large vessels and gastrointestinal tract, and even may be life-threatening (1,2). Environmental, infectious and genetic factors have been proposed to act as the main contributors in the outbreak of BD. The etiopathogenesis of BD has been investigated in many studies for a long time but the exact etiology and mechanisms of pathogenesis have not yet been clarified (1). Genetic researches showed strong asso-

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ciation with HLA-B51 and TNF-α, IL-10 *vs.* IL-23R gene polymorphisms were also indicated. However, the exact genetic mechanisms have not been described for all patients (1,3-5).

Recently, considering clinical and immunologic properties of BD, the disease is thought to be a cornerstone between autoimmune and inflammatory diseases. Association with HLA, immunologic properties and presence of autoantibodies support autoimmunity, however, clinical features and male predominance suggest inflammatory disease (1). Some studies assert that characteristics and severity of the disease have been changed over years. Also, subtypes of BD have been discussed (6,7). Behçet's disease does not have a specific diagnostic feature or a laboratory method, therefore clinical characteristics and symptoms are the main factors for management of BD. Thus, investigations of its prevalence and clinical features should be performed periodically in the countries with a high prevalence of BD to follow the changing dynamics of the disease, which may also lead to refinements in the unexplained pathogenesis of BD. From these aspects, also, cohort studies from different geographical regions are worthwhile.

Recently, family history has been thought to play an important role in the etiopathogenesis of BD and has been proposed to participate in diagnostic criteria, especially in pediatric BD (5,8,9). Clinical features of familial BD and increased frequency of some isolated manifestations of the disease in relatives of BD patients have been investigated in a few studies (9,10). Investigating the features of patients with different family histories may give an insight into understanding BD. In this study, we aimed to explore the effect of familial occurrence and family history of ROUs on demographic and clinical features of BD.

MATERIAL AND METHODS

The study included 141 patients with BD who attended Departments of Dermatology in Kayseri Gunes Hospital and Yozgat Bozok University Medical Faculty between 2006 and 2011. The hospitals were in two different cities in central Anatolia, Turkey. All patients were examined by dermatologists, ophthalmologists, and if necessary by internal medicine or physical and rehabilitation specialists, cardiovascular surgeon or neurologist. Establishment of diagnostic criteria was done according to the International Study Group for BD (11). Demographic data and clinical characteristics of all patients were evaluated retrospectively from their medical records. In addition, age at onset, duration of ROUs before diagnosis, and family history of BD and ROUs were evaluated. According to patient medical reports, a first degree relative with BD or ROUs was accepted as a positive family history. Patients were divided into three groups according to their family history: group I – patients with family history of BD with/without ROUs; group II – patients who had only ROUs in family history; and group III – patients with negative family history of BD and ROUs.

Pathergy testing was performed by a 12-gauge sterile needle puncture on the forearm and assessed by dermatologist at initial examination. Papule, pustule, or papule surrounded by adjacent erythema were considered as positive reaction.

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used on statistical analyses, while between-group comparisons were assessed by use of χ^2-test, Mann-Whitney U test and one-way ANOVA test.

RESULTS

Out of 141 patients, there were 71 (53.9%) male and 65 (46.1%) female patients, with a male to female ratio of 1.16. Their mean age was 33.8±9.69 and mean age at onset 29.77±8.56 years. The mean duration of ROUs before diagnosis of BD was 7.75 years. Pathergy positivity was present in 41.1% of patients and ROUs were obtained in all patients (100%). Genital ulcer was observed in 83%, erythema nodosum in 46.8%, acneiform eruption in 73.8%, superficial thrombophlebitis in 16.3%, extragenital ulcer in 10.6%, eye involvement in 33.3%, arthritis/arthralgia in 72.3%, neurologic involvement in 2.8% and large vessel involvement in 10.6% of all patients. There was no patient with gastrointestinal system involvement. Groups I, II and III consisted of 44 (31.2%), 45 (31.9%) and 52 (36.9%) patients, respectively. All 44 group I patients had both BD and ROUs, while 14 had only BD in their first-degree relatives. There was no statistically significant between-group difference according to sex, age and age at onset of the disease ($p>0.05$). Statistical analysis comparing differences in pathergy positivity and clinical manifestations of BD revealed no significant between-group difference ($p>0.05$). However, group I and group II patients had longer duration of ROUs before diagnosis of BD and more frequent extragenital ulcers than group III patients ($p<0.05$ and $p<0.01$, respectively). Demographic data, clinical manifestations and pathergy positivity of all groups are summarized in Table 1.

Clinical manifestations and pathergy positivity were evaluated according to sex. No statistically significant sex differences were detected in patient age, age at onset and duration of ROUs before diagnosis of BD. The frequencies of all clinical manifestations except for eye involvement and pathergy positivity

Table 1. Demographic features and clinical manifestations in patients according to family history

	Positive family history for BD (group I)	Positive family history for ROUs without BD (group II)	Negative family history for BD or ROUs (group III)	Total	p
Number of patients	44	45	52	141	
Male	27	21	28	76	0.498
Female	17	24	24	65	0.498
Mean (±SD) patient age (yrs)	34.38±9.78	33.26±10.79	33.9±8.74	33.85±9.69	0.952
Mean (±SD) patient age at BD onset (yrs)	29.38±8.65	28.80±8.9	30.94±8.65	29.7±8.56	0.217
Mean (±SD) duration of ROUs before diagnosis (yrs)	9.26±5.53	7.71±4.9	6.48±3.92	7.75±4.88	0.018*
Pathergy positivity	21	20	17	58	0.283
Genital ulcer	39	36	42	117	0.324
Erythema nodosum	22	26	18	66	0.065
Acneiform eruption	33	32	39	104	0.887
Superficial thrombophlebitis	7	10	6	23	0.363
Extragenital ulcer	1	10	4	15	0.007*
Eye involvement	16	15	16	47	0.845
Arthritis/arthralgia	36	28	38	102	0.117
Neurological involvement	2	2	0	4	0.3
Gastrointestinal system	0	0	0	0	-
Large vessel involvement	3	6	6	15	0.588

*statistically significant difference; BD = Behçet's disease; ROUs = recurrent oral ulcers

showed no significant differences between male and female patients either (p>0.05). Eye involvement and pathergy positivity were more common in male patients (p<0.01 and p<0.05, respectively). These data are shown in Table 2.

DISCUSSION

The epidemiology of BD has remarkable properties. The high prevalence of BD in ancient Silk Road has been known for a long time. However, the incidence of BD decreases among immigrants from high prevalence regions (5,12). So, environmental triggering factors seem to be as important as genetic susceptibility. On the other hand, a wide spectrum of clinical manifestations are observed even in patients with similar genetic background and environmental factors. Familial BD is important in the epidemiology, with the reported prevalence of 15.4% in Korea, 13.2% in Jews, 2.6% in China, 2.2% in Japan and 1% in Europe (5,7,13). Familial aggregations differ in various regions, especially familial cases are common in regions with a high prevalence of BD. Studies from Turkey show the prevalence of familial BD of 34%, 25.8%, 22.4%, 18% and 7.3% (3,9,14). Familial BD is more common in pediatric patients and frequencies of 30.7% and 47% have been reported in two studies (5,15). In one series, 12.3% of pediatric BD cases and only 2.2% of non-pediatric patients had a family history of BD (16). An investigation showed λs values of 11.4-52.5 for BD resembling the high sibling recurrence risk ratio in Turkey. However, it has been claimed that an increased prevalence of familial aggregation in juvenile BD may define a subgroup with stronger genetic effects (9).

In our study, familial BD was found in 44 (31.2%) patients and 30 of them also had a family history of ROUs. Five of our 141 patients were pediatric BD (age ≤16 years). One of them had a family history of BD, three patients had a family history of ROUs, and one patient had negative family history for BD and ROUs. Also, 31.9% of our patients had a family history of ROUs without BD. In a study from Turkey, the rate of familial BD was 12.2% and of family history of ROUs without BD 13.6% (14).

Recurrent oral ulcers are the major diagnostic criterion and a *sine qua non* of BD; they appear in almost all patients, and according to the general opinion, they frequently are the first systemic manifestation of the disease (17). However, ROUs are not specific for BD and there are numerous causes of ROUs. Recurrent oral ulcers may occur in 0.5% to 40% of the general population and clustering of familial cases were demonstrated (3,18-21). Behçet's disease is a common diagnosis in cases of ROUs with early onset and

Table 2. Demographic features and clinical manifestations in patients according to sex

	Female	Male	Total	p
Number of patients	65	76	141	0.498
Mean (±SD) patient age (yrs)	34.18±9.3	33.4±10.04	33.85±9.69	0.884
Mean (±SD) patient age at BD onset (yrs)	29.68±8.2	29.87±9,0	29.7±8.56	0.451
Mean (±SD) duration of ROUs before *diagnosis (yrs)*	7.7±4.92	7.67±4.83	7.75±4.88	0.260
Pathergy positivity	16	42	58	0.00*
Genital ulcer	58	59	117	0.553
Erythema nodosum	35	31	66	0.84
Acneiform eruption	50	54	104	0.276
Superficial thrombophlebitis	11	12	23	0.517
Extragenital ulcer	8	7	15	0.373
Eye involvement	15	32	47	0.013*
Arthritis/arthralgia	47	55	102	0.571
Neurological involvement	1	3	4	0.371
Gastrointestinal system involvement	0	0	0	-
Large vessel involvement	4	11	15	0.091

*statistically significant difference; BD = Behçet's disease; ROUs = recurrent oral ulcers

in presence of multiple oral ulcerations. In one study, no significant difference was recorded in the frequency of familial cases between ROUs and BD (20). In another study, patients with a positive family history showed an earlier age at onset of ROU episodes and more severe symptoms than patients with negative history (19). In a series study from Turkey, 47 of 1238 (3%) patients with ROUs were diagnosed as BD with a mean duration of 5.61 years (22). In a Korean study, 35 of 67 (52.2%) patients with ROUs were diagnosed as BD in 7.7 years (21). In our study, the mean duration of ROUs before the diagnosis of BD was 7.75 years.

Alli *et al*. mention that a high prevalence of isolated manifestations of the disease, such as recurrent orogenital ulcers or a positive skin pathergy test, was also observed among patient first-degree relatives who probably were low-penetrant carriers of predisposing genes. But, the high prevalence of ROUs in the general population should be taken into account. Additionally, they did not observe earlier age at onset in patients with a family history of BD or ROUs (14). It was consistent with our results. However, in one study, the age at onset was lower in familial BD (16). Another investigation revealed an early onset of familial BD with ocular involvement (7). Besides this, our patients with a family history of BD and/or ROUs had a longer duration of ROUs before the diagnosis of BD. It was compatible with the general belief that an early onset of ROUs with a family history of BD and ROUs is more likely to be a predictor of BD (8,15,20). Sporadic ROUs should be considered as an early predictor of probable BD in patients with a family history of BD and/or ROUs and they should be followed up carefully.

Alli *et al*. found no statistically significant relationship between activity scores and family history. However, the frequencies of clinical manifestations of familial and non-familial cases were not assessed (14). Nishiyama *et al.* report on the early onset of familial BD with ocular involvement but they did not assess the frequencies of all clinical manifestations either. They point out that a large-scale epidemiological study of familial BD patients is also needed to elucidate the etiology of the disease (7). In the current study, we aimed to explore the effect of familial occurrence and family history of ROUs on all clinical features of BD. The rates of pathergy positivity did not show any significant difference among the three groups with different family histories. We did not find any significant difference in most clinical features between patients with different family histories ($p>0.05$). Besides, patients with a family history of BD and/or ROUs had more frequent extragenital ulcers than patients with negative family history of BD and ROUs ($p<0.01$). Extragenital ulcer was found in 15/141 of our patients. One of the 15 patients with extragenital ulcer had a family history of BD with/without ROUs, ten patients had a family history of ROUs without BD, and four patients had negative family history of BD and ROUs. Extragenital ulcers are one of the cutaneous lesions of BD. Cutaneous lesions are an important feature of the disease and have been described by the International Study Group for Behcet's Disease as a major criterion for the diagnosis (11). Further reports on BD may assert the impact and specificity of extragenital ulcers in the diagnosis and genetic background.

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Some studies determined higher rates of pathergy positivity among male patients with BD (14,23). We also observed higher rates of pathergy positivity among males. In our study, the frequency of ocular involvement was also higher in males and it was consistent with some studies in the literature (23,24).

Herein we analyzed all demographic and clinical features of our patients with BD according to different family histories. We hypothesized that familial BD may present different clinical spectrum from a non-familial patient. Also, a patient with a family history of ROUs may have different clinical features of BD than a patient with negative family history. In the literature, a few studies investigated some features of familial BD (7,14), while some others report isolated manifestations of BD in relatives of BD patients (5,9,14). Indeed, BD has interrelated demographic, genetic and clinical properties (1,12). Interestingly enough, ROUs, which are the major feature as a diagnostic criterion for BD, also have interrelated demographic, genetic and clinical properties (21,25). Familial cases are important in the pathogenesis and prognosis of both diseases (5,7,14,20). However, ROUs do not show geographical clustering but show horizontal transmission (17). So, advanced studies are needed to clarify the relationship of BD and ROUs. Genetic analysis was not included in our study and this was an important limitation of the study. Additional studies including genetic testing of patients and their relatives may be worthy.

CONCLUSION

Our findings did not show any strong effect of familial occurrence or positive family history of ROUs on any clinical characteristic of BD. However, sporadic ROUs should be considered as an early predictor of probable BD in patients with a family history of BD and/or ROUs and they should be followed up carefully.

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