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Behçet's Syndrome in Iranian Azari People

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Abstract: Behçet's Syndrome (BS) is a chronic recurrent multisystemic inflammatory disorder characterized by oral and genital ulcers, ocular inflammation. Behçet's syndrome has a complex genetic etiology. However, epidemiological studies recommend that genetic factors have a significant influence to its pathogenesis, alike to other autoinflammatory disorders. Epidemiological statistics, clinical records and HLA typing were studied in Iranian Azari patients with Behçet's syndrome. This investigation considered HLA associations with BS and HLA with certain clinical characteristics, age and sex in the (Tabriz) Iran which has an ethnically homogeneous population. HLA-A and HLA-B typing was performed in 290 BS patients, conforming to International Study Group criteria and in 300 blood donors, as controls. Patient records were retrospectively reviewed and patients reassessed clinically. HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 presented significantly high frequencies in all patients. No other HLA type was associated. There was a significant HLA link with male sex in BS patients and Mean age (34±1.1) was determined. We present the frequency and correlation between Iranian Azari patients with Behçet's syndrome and particular HLA antigens. Ninety nine percent had mouth ulceration, 64% genital ulceration, 72% skin lesions and 52% ocular involvement. This study supports HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 immunogenetic predisposition in an ethnically homogeneous (Iranian Azari) population.

Key words: HLA antigens, Behçet's syndrome, HLA typing

INTRODUCTION

Behçet's Syndrome (BS) is known as chronic relapsing inflammatory disorder, manifesting with oral, genital and ocular lesions which may attack to the joints, skin, central nervous system and gastrointestinal tract (Kaneko *et al*., 2011). Behçet's syndrome has a complex genetic etiology. BS prevalence has been described worldwide with peculiar ethnic distribution and highest one in countries such as Turkey, Iran and Japan which are place on Silk Road (an ancient trading route between the Mediterranean and East Asia, where it is a main cause of morbidity) (Anonymous, 1990). Extensive Epidemiological studies about prevalence of the disease indicated that Turkey has the highest prevalence (0.08-0.42%) while the occurrence in Korea, China and Japan is on the order of 15-20 cases per 100,000, in the UK it is as low as 0.64 cases per 100,000 and also in Iran was reported 16.7 case per 100,000 populations (Salvarani *et al*., 2007).

The diagnosis of Behçet's Syndrome (BS) is based on clinical picture according to diagnostic criteria in the International Study Group's classification. Diagnosis requires recurrent oral ulcerations along with recurrent genital ulcerations and skin lesions, eye lesions and a positive pathergy test (Marshall, 2004) but HLA typing as a laboratory finding, can contribute to better diagnosis in these patients. The purpose of this study was to investigate whether immunogenetic predisposition is present in an ethnically homogeneous in Iranian Azeri patients with Behçet's syndrome and to analyses the epidemiology and clinical picture of subjects. We present the frequency and correlation between Iranian Azeri patients with Behçet's syndrome and particular HLA antigens.

MATERIALS AND METHODS

Patients: In a retrospective cohort study, 290 patients with Behçet's syndrome chose from outpatient of Imam Reza Medical Research and Training Hospital, Tabriz, Iran by referral from requests to rheumatologist physicians during a period of 4 years (from January 2009 through July 2012).

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Disease assessment: The diagnosis of Behçet's syndrome was based on the criteria of the International Study Group Criteria (ISG). Briefly, this required the presence of recurrent oral ulceration plus two of the following: recurrent genital ulceration, eye lesion (anterior or posterior uveitis), skin lesions (erythema nodosum, pseudofolliculitis or papulopustular lesions) or a positive pathergy test. Patients with incomplete disease were excluded from study and HLA typing was performed on patients with Iranian Azeri origin.

HLA typing: Peripheral blood lymphocytes were separated on a Ficoll-Hypaque density gradient. HLA tissue typing was performed by the standard two stages National Institute of Health micro-lymphocytotoxicity technique. The unrelated normal controls group consisted of 300 healthy voluntary blood donors to the Blood Transfusion, of whom all had HLA-A and HLA-B typing. Age and sex matched consecutively typed controls were chosen for each patient so that both patient and controls were typed at the same time using the same antisera.

Statistical analysis: Statistical significance between the relative frequencies of antigens in patients and controls was determined by Chi square (χ^2) and Fisher's exact tests with Yates's correction. Exact p values were corrected to avoid a type I error. Correction is performed by multiplying the exact p-value with the number of antigen frequencies tested. Any HLA association with certain clinical features, such as sex, age was evaluated. Age at diagnosis was defined as the age at which the ISG criteria for diagnosis were fulfilled. Statistical association with age was assessed by the Independent-Samples t-test procedure.

RESULTS AND DISCUSSION

The frequencies of the HLA antigens significantly increased in the patients in comparison to the controls. The numbers of patients with Behçet syndrome 290 ($p<0.01$) and HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 were significantly increased (Table 1). None of the other HLA antigens showed significant increased frequencies in BS. HLA-B5 was found in 61.9% of the patients compared to 1.3% of controls; relative risk = 3.517, $p<0.0001$. HLA-B35 was represented among Iranian Azeri patients with Behçet's syndrome, being found in 65.4% of the patients compared to 21.5% of controls; relative risk = 2.469 $p<0.05$ (Table 1). Clinical manifestations in 290 patients with Behçet's syndrome were based on the criteria of the International Study Group Criteria (ISG) (Table 2). The frequencies of the clinical manifestations in 290 patients were as follows in decreasing order, oral ulcer (99.2%), genital ulcer (64.0%), skin lesion (72.4%), ocular involvement (52.9%), arthritis (20.6%) gastrointestinal disease (21.1%) and neurological symptom (10.6%).

Table 1: HLA antigen frequencies in Iranian Azari patients with Behçet's disease

	Antigen frequency				
HLA antigen	Patient (%)	Control subject (%)	Chi square (χ^2)	Relative risk	Exact p-value
A1	47.1	54.4	0.794	0.864	0.302
A2	34.9	34.9	0.000	1.000	1.000
A3	46.7	51.7	0.320	0.905	0.480
A7	1.7	2.0	0.000	0.918	1.000
A8	2.1	4.7	0.390	0.609	0.110
A10	5.2	6.0	0.000	0.925	1.000
A11	55.7	58.4	0.059	0.947	0.668
A12	4.2	10.1	1.808	0.569	0.103
A24	27.3	30.9	0.164	0.915	0.641
A26	8.3	6.0	0.127	1.175	0.592
A27	3.1	5.4	0.208	0.721	0.515
A28	20.8	15.4	0.588	1.395	0.336
A30	8.7	6.0	0.212	1.201	0.592
A35	5.9	2.7	1.757	1.533	0.185
B5	61.9	1.3	84.171	3.517	0.000
B7	13.5	16.1	0.102	0.898	0.512
B8	13.1	18.8	0.824	0.794	0.247
B21	19.7	24.8	0.486	0.857	0.393
B27	9.7	17.4	1.916	0.685	0.095
B35	65.4	21.5	37.451	2.460	0.000
B39	4.5	2	0.358	1.403	0.499
B44	4.8	4.7	0.000	1.011	0.758
B51	42.6	4.7	37.704	2.396	0.000
B52	41.9	3.4	40.133	2.463	0.000
BW4	52.6	41.6	2.007	1.558	0.119
BW6	64.0	58.4	0.660	1.127	0.469
CW1	7.3	12.1	0.824	0.733	0.210
CW2	7.6	13.4	1.226	0.701	0.165
CW3	8.7	10.7	0.057	0.887	0.564
CW4	41.5	23.5	6.587	1.473	0.005
CW6	32.2	41.6	1.515	0.812	0.187

*HLA: Human leukocyte antigen, (HLA is a locus on chromosome 6 which encodes for a large number of HLA alleles like HLA-CW1, HLA -BW4 or HLA-B)

Table 2: Clinical manifestations in 290 patients with Behçet's syndrome. Results are given as number (%) of patients

Clinical manifestations	Positive (%)
Oral ulcer	99.2
Genital ulcer	64.0
Skin lesion	72.4
CNS disease	10.6
Ocular disease Uveitis	52.9
Gastrointestinal disease	21.1
Arthritis	20.6

HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 status and sex in Iranian Azari Behçet's disease were shown in Table 3. Two hundred eighty nine patients were included in this study. The male-to-female ratio was (61.2% male, 38.8% female), showing the male predominance. The mean age onset was 34.3±1.1 years and the most common age of onset was 32 year.

Typical Behçet's syndrome is easy to diagnose because of the triad of features: uveitis, recurrent aphthous and genital ulceration, but less complete cases are more complicated to differentiate. The most

Table 3: HLA-B status and sex in Iranian Azari Behçet's disease

		HLA-B5 statues		
Sex	Total (n = 290)	Positive (n = 180)	Negative (n =110)	Exact p-value
Male	178	102	76	
Female	112	78	34	0.36
		HLA-B35 statues		
Sex	Total (n = 290)	Positive (n = 190)	Negative (n = 100)	Exact p-value
Male	178	112	66	
Female	112	78	34	0.14
		HLA-B51 statues		
Sex	Total (n = 290)	Positive (n = 124)	Negative (n = 166)	Exact p-value
Male	178	69	109	
Female	112	55	57	0.48
		HLA-B52 statues		
Sex	Total (n = 290)	Positive (n=122)	Negative (n=168)	Exact p-value
Male	178	69	109	
Female	112	53	59	0.85
		HLA-CW4 statues		
Sex	Total (n = 290)	Positive (n=138)	Negative (n=152)	Exact p value
Male	178	87	91	
Female	112	51	61	0.54

substantial conclusion in this study is a highly significant association between HLA-B5, HLA-35 and Behçet's syndrome (corrected exact p value = 0.001) in Iranian Azeri which has an ethnically homogeneous population in comparison to the other ethnic groups that there was not any report previously. Our data differ from those of others who found no association between Behçet's syndrome and HLA-B52, HLA-B35 and HLA-CW4. However, the predisposing effect of B5, B51 and B52 in our group of patients resembles to other ethnic group patients (Arber *et al*., 1991; Kilmartin *et al*., 1997). Subjects with HLA-51, HLA-B52 and HLA-CW4 are considered at great risk of developing Behçet's syndrome.

This study supports HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 immunogenetic predisposition in ethnically homogeneous population of Iran and the current data indicate that the presence of HLA-B35 in a selected patient population may serve as an additional clue for the diagnosis of Behçet's syndrome in symptomatic patients. Pervious study in the latest analysis of 6903 BD patients and 5012 controls with Iranian Persian ethnic population showed that the incidence of B5 in BD patients was 52.9% and in controls 39.8%, for B51 for BD patients 64.6% and for controls 4.7% (Shahram *et al*., 2004). However, HLA-B7 and B27 were negatively associated with the disease in contrast to other ethnic group. For instance, HLA-B27 study in Iranian Persian ethnic population was showed in 481 patients (8.6%), thus differs from other reports which showed a raise in British patients (Bettencourt *et al*., 2008), including an incidence of 25% of HLA-B27 positivity in BD independent of the clinical type of presentation (Ahn and Park, 2007).

CONCLUSION

The current data indicate highly significant HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 association with BD in Iranian Azari people, with a high relative risk. The presence of these HLA (Human Leukocyte Antigen) in a selected Iranian Azeri ethnic population may serve as an additional clue for the diagnosis of Behcet's syndrome in symptomatic patients. This study can support a HLA-B5, HLA-B35, HLA-51, HLA-B52 and HLA-CW4 immunogenetic predisposition in an ethnically homogeneous from the Silk Route.

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