Original Article

BEHCET'S DISEASE IN IRAN, ANALYSIS OF 5,059 CASES

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BACKGROUND—*Iran is among the countries with rather high prevalence of Behcet's disease (BD). We present here our latest data on different aspects of the disease.*
MATERIALS AND METHODS—*The present investigation is a prospective cohort study carried out on the data of patients presented in our BD registry during the past 28 years. The data were collected on a standard protocol comprising 100 items. These items included demographic features (such as sex, age of onset, age of diagnosis, date of the first visit, and ethnic origin), type of the presentation, different clinical manifestations of the disease, and paraclinical findings (including CBC and platelet count, Erythrocyte sedimentation rate, VDRL/RPR test, urinalysis, HLA typing, and Pathergy skin test). A confidence interval (CI) at 95% was calculated for each item.*
RESULTS—*A total number of 5,059 patients were analyzed. The annual incidence rate was 280 patients in the last 5 years. The male/female ratio was 1.19/1 and the mean age at onset was 26 ± 9.8 (CI: 0.3). As the first manifestations, oral aphthosis (OA) was the most frequent (81%, CI: 1.1). The prevalence of variuos manifestations were OA: 97% (CI: 0.5), genital aphthosis: 65% (CI: 1.3), skin: 69% (CI: 1.3), ocular: 56% (CI: 1.4), joint: 34% (CI: 1.3), CNS: 3% (CI: 0.5), vascular: 8.5% (CI: 0.8), GI: 8% (CI: 0.8), and epididymitis: 10% (CI: 1.1). The laboratory findings were as follows: high ESR: 53% (CI: 1.4), urine abnormality: 10% (CI: 0.9), positive pathergy test: 57% (CI: 1.4), HLA B5: 52.5% (CI: 1.4), HLA B51: 34% (CI: 5.1), and HLA B27: 9% (CI: 0.8).*
CONCLUSION—*Recent survey in Iran revealed a remarkable decrease of the incidence rate of BD and a tendency toward milder forms of the disease. Our data show more similarity with those of Turkey and Japan than with the western parts of the world.*

Keywords: ***Behcet's disease; vasculitis; epidemiology; Iran.***

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INTRODUCTION

Behcet's disease (BD) is a multisystem disease classified among vasculitides[1] and there are several reports on this disease from many countries. BD occurs most commonly in countries along the silk route.[2,3] Besides the different geographic distribution of the disease, its clinical manifestations also differ throughout the world.[2,3] The higher frequency of positive Pathergy test and HLA B5 in eastern countries, gastrointestinal involvement in Japan, and amyloidosis in Mediterranean countries can be emphasized.[1 – 4] Iran is among the countries with rather a high prevalence of the disease.[4] The epidemiological survey, providing data on different aspects of the disease, has been continuously carried out since 1975 in our center. We present here our latest data on a large number of Iranian patients.

MATERIALS AND METHODS

This study was done prospectively on a cohort of registered patients with the diagnosis of Behcet's disease referred to our BD unit during the past 28 years (from 1975 to March 2003). The registered patients included nearly the majority of diagnosed cases in Iran. All patients were seen in a multidisciplinary clinic by the same team of physicians comprising rheumatologists, ophthalmologists, and dermatologists. Patients were seen by the affiliated neurologists and gastroenterologists when needed. Diagnosis was based on the clinical picture of the disease and the clinical judgment of at least two rheumatologists of the group, and not only on a particular diagnostic criteria. The diagnosis was double checked by either

the first author or professor Davatchi before entering the BD registry. The majority of the cases however, were classified by at least two of the major sets of diagnostic criteria.[5-11]

A computerized form with 100 clinical and paraclinical parameters was designed for each patient. These parameters included demographic features (such as sex, age of onset, age of diagnosis, date of the first visit, and ethnic origin), type of the presentation, different clinical manifestations of the disease, and paraclinical findings. The latter included CBC and platelet count, Erythrocyte sedimentation rate (ESR), VDRL/RPR test, urinalysis, HLA typing for HLA B5 and HLA B27, and pathergy skin test; that were done systematically for all of the patients at the first visit. The data were fed into an electronic database especially developed for this purpose in our center. According to the severity of the disease, patients were followed up once every month to once every year. The database was updated every week after each visit of the patients. A confidence interval (CI) at 95 percent for each item, and a standard deviation (SD) for the means and the percentages was calculated.

RESULTS

The annual incidence rate of BD, in the past 5 years, was around 280 patients per year. The mean disease duration was 9.3 years (SD: 7.1), and the mean follow up was 3 years (SD: 4). Positive familial history for BD was present in 5.9 % (CI: 0.9) of the patients, mostly (66.5%, CI: 7.4) in their first degree relatives (parents, children, or siblings). In 50.1% (CI: 1.9) of the patients a positive history of oral aphthosis was also present, 89.4% (CI: 1.7) in the first degree relatives.

Sex and age distribution

Fifty-four percent of our patients were male (CI: 1.4). The male to female ratio was 1.19/1. It was interesting that the sex difference was only significant during the third and forth decades of life (Figure 1). The disease onset was mainly in the third decade of life, but with a range between 1 to 70 years (Figure 1). The mean age at onset of the disease was 26 years (SD: 9.8, CI: 0.3). There was no significant difference between the males and females in the mean age of onset (t: 0.360, p = 0.72). Most of the patients (85.7%, CI: 1) were in the adult group. In the remaining patients, although the disease onset was before the age of 16, the majority completed their disease in adulthood (9.6%, CI: 0.8). Among those who completed their disease in childhood, 1.5% (CI: 0.3) were diagnosed in adulthood. Only in 3.1% (CI: 0.5) the diagnosis of BD was made during the childhood.

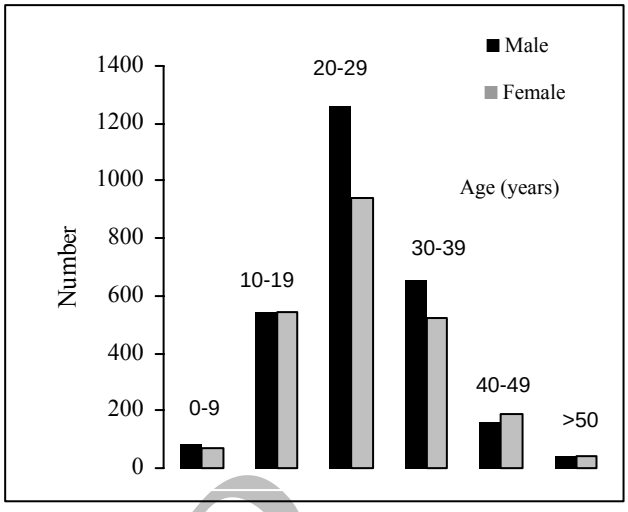

Figure 1. Age and sex distribution in Behcet's disease.

As the first manifestation, oral aphthosis was the most frequent one, presenting in 80.7% (CI: 1.1) of the cases. Genital aphthosis was present in 10.2% (CI: 0.8), mostly accompanied by oral aphthosis. Only in 2.3% (CI: 0.4) of the cases it was seen alone with no other symptoms. Ocular lesions, as uveitis in 9.3% (CI: 0.8), and retinal vasculitis in 0.4% (CI: 0.2), were the other presenting signs of the disease. Joint involvement in 5.1% (CI: 0.6), and the other manifestations (mostly skin lesions) in 8.2% (CI: 0.8), were the other initial manifestations of the disease.

Major manifestations (Table 1)

The mucous membrane involvement, either oral or genital, was present in 97% (CI: 0.5) of the patients. Oral aphthosis was the most frequent symptom, seen in 96.8% (CI: 0.5) of the patients. Genital aphthosis was seen in 65.3% (CI: 1.3). Only in 14 cases it remained the unique mucosal lesion of the disease, while in the remaining it was associated with oral aphthosis.

Skin lesions were present in 69.3% (CI: 1.3) of the patients; pseudofolliculitis in 60.6% (CI: 1.3); and erythema nodosum in 22.2% (CI: 1.1) of the cases. These two lesions are classified as a major sign in most existing diagnostic criteria.[5-11] Other skin lesions were seen rarely (6.4%, CI: 0.7). They included a wide range of lesions such as wheals, subcutaneous nodules without surrounding inflammatory reactions, Behcet's cellulitis, and notably skin aphthosis which is highly suggestive of the disease.[12]

Ocular lesions were seen in 55.6% (CI: 1.4) of our patients; anterior uveitis in 41% (CI: 1.4); posterior uveitis in 44.4% (CI: 1.4); and retinal vasculitis in 30.5% (CI: 1.3). The classic ocular lesion in BD, panophthalmitis involving all these 3 parts, was seen in 21.2% (CI: 1.1) of the patients. Panuveitis was present in 12% (CI: 0.9). Cataract was seen in 14% (CI: 1) and conjunctivitis in 6% (CI: 0.7) of the patients, although both are nonspecific for the disease.

Minor manifestations (Table 2)

Joint involvement was seen in 34.3% (CI: 1.3) of the patients. The most characteristic form was asymmetric oligo-arthritis, seen in 16.6% (CI: 1). This form usually involves the large joints of lower limbs. Inflammatory arthralgia with morning stiffness lasting not more than 1 hour, was reported by 15.2% (CI: 1) of the patients. Monoarthritis, mainly involving the knee joints, was seen in 7.6% (CI: 0.7). The other form (ankylosing spondylitis) was seen in 1.5% (CI: 0.3) of our cases. This is 15 times greater than its prevalence in the general population of Iran.

Neurological manifestations were fortunately rare in Iranian patients. It was seen only in 3.2% (CI: 0.5) of the cases, and most of them were due to central involvement (3%, CI: 0.5). The most common presenting syndrome was stroke involving mainly the brain-stem with acute mode of onset. Peripheral nervous system lesions were present only in 0.2% (CI: 0.1).

Large vessel involvement was seen in 8.5% (CI: 0.8) of the patients. Venous involvement was seen more frequently (8.2%, CI: 0.8), including deep vein thrombosis in 6% (CI: 0.7), superficial phlebitis in 2.3% (CI: 0.4), and large vein thrombosis in 1% (CI: 0.3) of the cases. Arterial involvement was rare (0.5%, CI: 0.2), and aneurysm was more common than thrombosis (25 aneurysms and 4 thrombosis). Thirteen patients showed both arterial and venous involvement. We encountered 2 cases with pulse weakness without any evidence of arterial thrombosis or aneurysm.

Gastrointestinal manifestations were uncommon, with overall prevalence of 7.6% (CI: 0.7). Gastroduodenitis was seen in 2.7% (CI: 0.4), peptic ulcers in 1.5% (CI: 0.3), diarrhea in 2% (CI: 0.4), rectal bleeding in 0.8% (CI: 0.2), and abdominal pain mimicking a surgical acute abdomen in 1.7% (CI: 0.4) of the patients. The true gastrointestinal involvement of BD, that is vasculitis of the terminal ileum and ileo-cecal region, was actually rare in Iran.

Pulmonary involvement was rare, seen only in 41 patients. The most frequent lesion was infections (17 cases). Vasculitis (10 cases), pleural effusion (6 cases), and embolism (6 cases) were those that seemed to be related to the disease. We may therefore consider the true prevalence of pulmonary involvement of BD to be 0.5% (CI: 0.2). Cardiac involvement was even rarer than pulmonary lesions, seen in only 26 patients (0.5%, CI: 0.2). We encountered ischemic heart disease in 10, valvular lesions in 7, and pericarditis in 6 of our patients. Direct relation to the disease was not confirmed in all.

Among the other manifestations, epididymo-orchitis was the most important, seen in 10.3% (CI: 1.1) of the males. Headache was reported by 7.1% (CI: 0.7). It included cases that could not be attributed to CNS or ocular involvement. Hepatosplenomegalia was rarely seen (0.5%, CI: 0.2). In 1.6% (CI: 0.3) of the patients an overlap or association with another autoimmune or collagen vascular disease was present.

Laboratory findings (Table 3)

Erythrocyte sedimentation rate (ESR) was normal during the disease course in most of the patients (46.6%, CI: 1.4). It was between 20 and 49 in 36% (CI: 1.4), between 50 and 100 in 15.8% (CI: 1), and >100 in 1.6% (CI: 0.4) of the patients. Urinary abnormalities were detected in 10.4% (CI: 0.9) of the patients. Hematuria was seen in 4.8% (CI: 0.6), proteinuria in 2.2% (CI: 0.4), leukocyturia in 5.4% (CI: 0.6), and urinary casts in 0.3% (CI: 0.2). They were transient in most of the cases, and only in 14 cases kidney biopsy was needed. The histological findings were compatible with mesangial proliferative glomerulonephritis (PGN) in 3, focal and diffuse PGN each in 5 cases. Amyloidosis was present only in 2 of our patients.

Pathergy test was positive in 57.4% (CI: 1.4), HLA B5 in 52.5% (CI: 1.4), and HLA B27 in 9.1% (CI: 0.8) of the patients. Typing for HLA B51 was done in 380 patients and was positive in 33.9% (CI: 5.1) of them False positive reaction for syphilis (VDRL or RPR test) was seen in 1.5% (CI: 0.4) of the patients.

Table 1. Major manifestations of Behcet's disease.

Manifestation	%	CI*
Oral aphthosis	96.8	0.5
Genital aphthosis	65.3	1.3
Skin lesions	69.3	1.3
* Pseudofolliculitis	60.6	1.3
* Erythema nodosum	22.2	1.1
Eye involvement	55.6	1.4
* Anterior uveitis	41	1.4
* Posterior uveitis	44.4	1.4
* Retinal vasculitis	30.5	1.3

*CI: Confidence interval at 95%

Table 2. Minor manifestations of Behcet's disease.

Manifestation	%	CI*
Joint	34.3	1.3
Neurological	3.2	0.5
* Central	3	0.5
* Peripheral	0.2	0.1
Large vessel	8.5	0.8
Gastrointestinal	7.6	0.7
Pulmonary	0.5	0.2
Cardiac	0.5	0.2

*CI: Confidence interval at 95%.

Table 3. Laboratory findings in Behcet's disease.

Laboratory finding	%	CI*
High ESR	53.4	1.4
Abnormal urine	10.4	0.9
* Proteinuria	2.2	0.4
* Hematuria	4.8	0.6
* Casts	0.3	0.2
Positive Pathergy test	57.4	1.4
Positive HLA B5	52.5	1.4
Positive HLA B51	33.9	5.1
Positive HLA B27	9.1	0.8
False positive VDRL	1.5	0.4

*CI: Confidence interval at 95%.

Disease classification

The most sensitive diagnostic criteria in Iranian patients was the classification tree[11] (97.3%, CI: 0.4). The sensitivity of other sets of diagnostic criteria were: Mason and Barnes criteria[5] 67.5% (CI: 1.3), O'Duffy criteria[6] 71.5% (CI: 1.2), International criteria[7] 81.8% (CI: 1.1), Dilsen criteria[8] 85.8% (CI: 1), Japan criteria[9] 87.4% (CI: 0.9), and Iran criteria (traditional format)[10] 92.5% (CI: 0.7).

DISCUSSION

There are many reports on clinical manifestations of BD from different parts of the world.[13-37] Clinical symptoms vary in those reports, but the variation is only on the frequency of symptoms, rather than the different kind of manifestations (Table 3). Due to this discrepancy some authors think BD is a syndrome rather than a disease.[38] Some separate BD of the Silk Road from the BD seen in other parts of the world.[39] The observed difference may have several explanations:

It may be due to different referra l patterns depending on the subspecialty of the authors. For example, in an ophthalmology center the percentage of ocular lesions is higher than expected. Different disease duration in the patients reported may be another cause for difference. As the higher the disease duration, the higher the possibility of more organ involvement in the course of the disease.[40] The statistical bias of small number of patients in most reports must be noticed. As they are actually case studies and, therefore, subject to bias inherent to this kind of study. The difference is less in nationwide surveys of BD in the world such as the surveys done in Japan,[13] Korea,[14] Germany,[33] and Iran.[4] We must also mention the role of different ethnic background (partly due to the presence of HLA B5 as a susceptibility gene for the disease) and geographical distribution.[1-4] Another important factor may be the difference in patient selection rather than racial or geographical differences. An epidemiological study done in a village in Turkey demonstrated great variation between the field results and the hospital based results where the authors work.[41]

Behcet's disease is not rare in Iran. The annual incidence rate was around 280 patients per year in our registry. Nearly all patients in Iran, diagnosed as having BD, are sent to our unit for confirmation of the diagnosis and further evaluation. Therefore comparison of our data (which reflects the real picture of the disease in Iran) with other reports may be interesting (Table 4). Our data show more similarity with those of Turkey[26] and Japan[13] than with the western parts of the world. This may be partly due to the presence of HLA B5 as a susceptibility gene for the disease.

The prevalence of major manifestations of the disease is nearly the same in these countries. This is also true for the frequency of positive pathergy test, necessitating it to be a major diagnostic tool in some sensitive sets of diagnostic criteria for the disease.[7-11] Fortunately, some minor but important manifestations of the disease like CNS, gastrointestinal, and vascular manifestations (notably large vessels involvement) were less encountered in Iran.

Recent survey in Iran revealed a remarkable decrease in the incidence rate of BD and a tendency toward milder forms of the disease as noticed in previous studies. This may have many explanations such as changing pattern of the disease, inclusive of milder forms of the disease, and finally the impact of new treatments in the course of the disease.[42]

Table 4. Distribution of Behcet's disease clinical symptoms in the world.

Country	No.	OA	GA	Skin	Eye	Joint	CNS	GI	Vas	Epid
Iran	5059	97	65	69	56	34	3.2	8	8.5	10
Japan[13]	3316	98	73	87	69	57	11	16	9	6
Korea[14]	1527	99	83	84	51	38	4.6	7	1.8	0.6
China[15]	138	99	86	63	42	50	10	15	10	—
India[16]	58	90	78	64	43	71	—	—	10	—
Saudi Arabia[17]	119	100	87	57	65	37	44	4	25	4
Iraq[18]	100	100	91	74	39	49	13	7	21	22
Jordan[19]	200	99.5	86.5	90.5	42	47	38.5	17	—	27
Lebanon[20]	100	95	78	53	63	65	14	10	9	2
Israel[21]	91	100	77	79	52	78	14	15	26	—
Egypt[22]	274	92	76	39	76	50	26	10	—	16
Algeria[23]	58	100	97	93	31	12	14	7	30	4
Tunisia[24]	200	100	80	—	60	50	20	—	—	—
Morocco[25]	673	100	84	—	67	57	14	—	19	—
Turkey[26]	2147	100	88	—	29	16	2.2	2.8	11	—
Tadjikistan[27]	36	100	71	79	49	44	14	—	14	—
Russia[28]	35	100	89	89	40	71	14	37	37	4
Greece[29]	101	100	78	75	73	54	20	4	11	13
Italy[30]	155	98	73	86	92	77	17	34	18	19
Portugal[31]	127	98	75	—	87	55	—	—	—	—
Spain[32]	38	100	91	73	35	62	17	5	19	—
Germany[33]	415	98	65	74	51	53	—	—	—	—
France[34]	73	97	62	74	55	94	28	18	—	1
England[35]	419	100	89	86	68	93	31	7	22	—
USA[36]	164	98	80	66	70	42	21	8	19	2
Brazil[37]	81	100	71	65	51	64	—	—	—	7

No.: Number of case; OA: Oral aphthosi; GA: Genital aphthosis; Eye: Ocular lesions; CNS: Central nervous system involvement; GI: Gastrointestinal manifestations; Vas: Vascular involvement ; Epid: Epididymitis.

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