

BEHÇET'S DISEASE

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Abstract- Behçet's disease (BD) which is classified among vasculitides is a systemic disease with various manifestations. It progress by attacks and remissions. Till now, two nationwide surveys of BD from Iran and Japan and 4 major case series from Turkey, Korea, Morocco and England have been reported. Clinical picture of BD is dominated by mucous membrane manifestations, including oral aphthosis - seen in 96.8% of patients in Iran, 98.2% in Japan, 100% in Turkey, 97.5% in Korea, 100% in Morocco and 100% in England- and genital aphthosis which is seen less frequently- 65.3% in Iran, 73.2% in Japan, 88.2% in Turkey, 56.7% in Korea, 83.5% in Morocco and 89% in England. Skin aphthosis is not frequent but it is the most characteristic lesion of BD. Erythema nodosum is seen more frequently in China and Korea. Ocular manifestations include anterior uveitis, posterior uveitis and retinal vasculitis. Joint Manifestations include arthralgia, monoarthritis, oligo/poly arthritis, and ankylosing spondylitis. Other presentations include neurological, gastrointestinal and cardiopulmonary manifestations, vascular involvement, orchitis and epididymitis. Erythrocyte sedimentation rate is usually elevated. Urinary abnormalities are infrequent and transient. Pathergy test was positive in 57.4% of patients in Iran, 44% in Japan, 57% in Turkey, 40% in Korea, 68% in Morocco and 32% in England. Lesions usually heal without sequela, except for eyes, brain, and vascular system. The major cause of morbidity is the ocular lesion, which leads to severe loss of vision or blindness.

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Key words: Behçet's disease, clinical manifestations, muco-cutaneous manifestations, aphthous ulcers

INTRODUCTION

Behçet's disease (BD) was originally a disease of the Silk Road. It was rarely seen in the northern part of Europe, in the American continent, and especially in the southern hemisphere. Due to immigrations, BD is now seen everywhere in the world.

BD is classified among vasculitides but its clinical picture is very distinctive from other vasculitides and can be easily differentiated. There are many reports on clinical manifestations of BD from different parts of the world. The majority are case series reports. There are actually two nationwide

surveys of BD, one from Iran (1) and the other from Japan (2). Although the two countries are far from each other and their populations are racially different, the difference between their clinical pictures is not striking (3). Each of these studies was done on a great number of patients, 3153 patients in Iran and 3316 patients in Japan. The comparison of case series with the nationwide surveys is difficult because of the difference in patients' selection. There are 4 major case series in the world, Turkey with 2147 patients (4), Korea with 1155 patients (5), Morocco with 673 patients (6), and England with 419 patients (7). Other series are based on less than 200 patients (8-26). Looking at reports from all over the world, it appears that the clinical picture varies from one to another. These differences have led some authors to stipulate that BD is a syndrome rather than a disease. However, difference in selection methods and clinical settings may explain the majority of these variations.

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Although the diagnosis is usually easy for an expert, it becomes difficult for non experienced physicians. The majority of disease manifestations is not specific and can be seen frequently in other diseases, or even in the normal population. Diagnostic criteria can be of help in these cases.

EPIDEMIOLOGY

BD is mainly seen along the Silk Road. The prevalence is much higher in countries bordering the Silk Road than in others. The highest prevalence is seen in Japan, Korea, China, Iran, and Turkey. The prevalence for 100,000 inhabitants was 13.4 in Japan, 14 in China, 16.7 in Iran, and 80 to 370 in Turkey. There is no exact figure from Korea. The prevalence was 1.2 in Kuwait, 20 in Saudi Arabia, 7.6 in Egypt, 7.5 in Spain, 2.26 in Germany, 2.5 in Italy, 1.5 in Portugal, 0.64 in UK (Yorkshire County), and 5 in USA (Minnesota, Olmsted County) (27-28).

There are controversies on the origin of BD, on whether it went from East to West on the Silk Road, or from West to East. The higher prevalence of BD in the eastern part of the Silk Road (Japan and China) compared to the western part (Portugal, Spain) is in favor of the eastern origin of the disease.

The rarity of BD in Japanese immigrated to Hawaii shows the importance of environmental factors. Iran is situated in the middle of the Silk Road and was from the ancient times the crossroad between east and west. Its population is comprised of 75.4% Caucasians, 22% Turks (East Asian origin) and 2.6% Semites. The prevalence of BD in Turks is 2 times higher than in Caucasians or Semites (29).

Age and sex

The sex distribution varies greatly depending on the series and countries. The male to female ratio was 0.98 in Japan, 0.63 in Korea, 1.19 in Iran, 1.03 in Turkey, 1.8 in India, 3.4 in Saudi Arabia, 4.9 in Kuwait, 3 in Iraq, 2.8 in Jordan, 1.3 in Lebanon, 2 in Morocco, 0.64 in Israel, 3.67 in Russia, 1.42 in Greece, 2.4 in Italy, 1 in Germany, 0.5 in Spain, 1 in Portugal, 0.6 in UK (Yorkshire), 0.36 in UK (Scotland), 1.4 in Ireland, 0.67 in Sweden and 0.69 in Brazil.

There was less variation in the age of onset from different reports: 35.7 in Japan, 29 in Korea, 26 in Iran, 25.6 in Turkey, 33.1 in India, 29.3 in Saudi Arabia, 20.4 in Iraq, 30.1 in Jordan, 26 in Lebanon, 30.7 in Israel, 26.2 in Egypt, 36.7 in Russia, 29 in Greece, 25 in Italy, 24.5 in Germany, 25.7 in Portugal, 24.7 in UK (Yorkshire), 20.8 in Ireland, 33 in Sweden, and 40 in Brazil. For the great majority of countries the age of onset was in the third decade of life.

CLINICAL MANIFESTATION

The clinical picture of BD is dominated by mucous membrane manifestations (oral and genital aphthosis), skin manifestations (pseudofolliculitis, erythema nodosum, and skin aphthosis), and ophthalmological manifestations. Table 1 summarizes the data from different countries. The data from Iran are driven from the latest published report on 5059 patients (30).

Mucous Membrane Manifestations

They are mainly oral and genital aphthosis, but other lesions can be seen. Oral aphthosis (OA) is the most frequent and constant manifestation of BD. It is seen in 96.8% of patients in Iran (Confidence Interval: 0.5), 98.2% in Japan (CI: 0.5), 100% in Turkey, 97.5% in Korea, 100% in Morocco and 100% in England. OA is not specific to BD and can be seen in other diseases like AIDS, ulcerative colitis, Crohn disease and systemic lupus erythematosus.

The elementary lesion is a well-defined and painful round or oval ulceration. It has a white yellowish necrotic base, surrounded by a red areola. The number of aphthous lesions varies from one attack to another. Sometimes it is isolated, but most of the time two or more lesions are seen together. The diameter of lesions varies from one attack to another, from 1 to 20 mm, with a tendency to decrease under the treatment. The lesions heal spontaneously in one or two weeks, without any treatment, but they have a high tendency to recur. The interval between recurrences varies from one attack to another, from few days to several months, and sometimes more.

Table 1. Distribution of Behçet's Disease clinical symptoms in the world

	No.	OA	GA	Skin	Oph	Joint	CNS	GI	Phl	Epid
Japan ²	3316	98	73	87	69	57	11	16	9	6
Korea ⁵	1155	98	57	61	29	24	5.7	4		
China ⁸	98	100	89		21.4	30.6	9.2	36		
India ⁹	58	90	78	64	43	71			10	
Saudi Arabia ¹⁰	119	100	87	57	65	37	44	4	25	4
Iraq ¹¹	58	100	100	83	35	31	19	3.3	33	14
Jordan ¹²	150	100	85	90	46		28	20	29	28
Lebanon ¹³	100	95	78	53	63	65	14	10	9	2
Israel ¹⁴	41	98	88	88	76	29	29		37	6
Egypt ¹⁵	274	92	76	39	76	50	26	10		16
Algeria ¹⁶	58						14	5	21	
Tunisia ¹⁷	200	100	80		60	50	20			
Morocco ⁶	673	100	84		67	57	14		19	
Iran ³⁰	5059	97	65	69	56	34	3.2	7.6	8.2	5.6
Turkey ⁴	2147	100	88		29	16	2.2	2.8	11	
Tadjikistan ¹⁸	36	100	71	79	49	44	14		14	
Russia ¹⁹	35	100	89	89	40	71	14	37	37	4
Greece ²⁰	90	100	77	74	71	56	20			11
Italy ²¹	155	98	73	86	92	77	17	34	18	19
Portugal ²²	127	98	75		87	55				
Spain ⁵⁵	38	100	91	73	35	62	17	5	19	
Germany ²³	196	99	75	76	59	59	13	16		16
France ²⁴	73	97	62	74	55	94	28	18		1
England ⁷	419	100	89	86	68	93	31	7	22	
USA ²⁵	164	98	80	66	70	42	21	8		2
Brazil ²⁶	81	100	71	65	51	64				7

Abbreviations: No, Number of cases; OA, Oral aphthosis; GA, Genital aphthosis; Oph, Ophthalmologic Manifestations; CNS, Central nervous system involvement; GI, Gastrointestinal manifestations; Phl, Phlebitis; Epid, Epididymitis.

OA may be localized everywhere on the oral mucosa with the following frequency order: lips, cheeks, tongue, gingiva, palate, tonsils, and pharynx. Different forms of oral aphthous lesions may be seen together at the same time. Giant aphthous lesions are rare in oral mucosa, but more frequent in genitalia.

Genital aphthosis (GA) is less frequently seen. It is detected in 65.3% of patients in Iran (CI: 1.4), 73.2% in Japan, 88.2% in Turkey, 56.7% in Korea, 83.5% in Morocco, and 89% in England. The clinical picture resembles OA, except that lesions are usually larger, heal more slowly and recur less frequently. In females they are often larger than 10 mm, and deeper than OA. They are localized on the

vulva, vagina, and rarely cervix. The giant aphthous lesion of the vulva is frequent, causing dysfunction and leaving sometimes indelible cicatrix. In males, GA is often seen on the scrotum, but may be seen also on the shaft of penis or on the meatus. Sometimes they become giant lesions.

There are other forms of mucous membrane manifestations (31). Anal aphthosis has the same characteristic as genital aphthosis. The lesion is external and close to the sphincter. Conjunctival aphthosis is small and ephemera, and missed most of the times. Ulceration and erosions are different from aphthous lesions as they have different clinical characteristics. They are often seen with aphthosis,

but are sometimes isolated and difficult to diagnose. The ulceration can produce multiple and various shapes without a specific characteristic (fissural form, punctuated form, slashed form, open book like, superficial ulceration and giant ulceration). These lesions are seen rarely. Without histological proof, the superficial and confluent forms are difficult to differentiate from the early stage of pemphigus vulgaris. Erythema usually surround aphthous lesions, but can also be isolated involving a large surface of the oral mucosa. Purpura and hemorrhagic lesions are very rare. They may be isolated or be seen with other lesions. They are usually small and round, but can also become widespread like a superficial hemorrhage.

Skin Manifestations

They are seen in 69.3% of patients in Iran (CI: 1.3), 87.1% in Japan, 60.6% in Korea, and 86% in England. They have various forms. Pseudo-folliculitis, erythema nodosum, and the pathergy phenomenon are the most classic.

Pseudo-folliculitis (Behçet's pustulosis) is a dome shaped (non-acuminated) sterile pustule on a round erythematous-edematous base. It is seen in 60.6% of patients in Iran (CI: 1.3). It is mainly located on the lower limbs and pubis, but may be seen everywhere, even on the palmo-plantar skin. When it is situated on the face, trunk, and back, it can be mistaken with acne vulgaris by a non-experimented eye.

Small round erythematous-edematous lesion is characterized by a round and slightly painful weal on the skin. It resembles Behçet's pustulosis, but without a pustule in its center.

Skin hypersensitivity to traumatism (pathergy) is a frequent phenomenon. A skin trauma like needle prick will produce a papule or a pustule, surrounded by an erythematous reaction. The pathergy test uses this phenomenon for diagnosis purpose. The skin is punctured with a 25 or 21-gauge needle, perpendicular or diagonally to the skin. The reaction is best seen 24 to 48 hours after the trauma. In Western countries, especially in England and in the United State, the frequency of positive pathergy test is lower than in Eastern countries. The pathergy phenomenon is not constant and may appear or disappear during the course of the disease (32).

Pathergy phenomenon is frequently seen in Iran, 57.4% of patients (CI: 1.5). It is reported in 44% of patients in Japan, 40% in Korea, 56% in Turkey, 68% in Morocco, and 32% in England.

Skin aphthosis is not frequent but it is the most characteristic lesion of BD. It is characterized by a yellowish narcotizing punched out painful ulceration. It is seen near genital areas, on the inner side of the thigh, axilla, submammary space, interdigital spaces, buttock, peri-anal skin, and the trunk. Skin aphthosis usually leaves a round atrophic scar after healing.

Small nodules are indurated and painful dermis nodules. They are more frequently seen on the hands than lower limbs, but can also be seen on other parts of the body. Behçet's cellulitis has been mistaken in the past with Sweet syndrome. The biopsy of Behçet's cellulitis always shows a vasculitis, not a neutrophilic dermatitis as in Sweet syndrome (33). It is a painful, large and round erythematous-edematous lesion. It is usually localized on the lower limbs, but sometimes on the upper limbs or on the face. Pyoderma gangrenosum like lesion is an exceptional lesion. It is a large superficial painful expanding ulceration, usually localized on the buttock and the lower limbs.

Among subcutaneous lesions of BD, erythema nodosum is the most important. It is rather frequent, and is a relapsing lesion. It is characterized by painful multiple subcutaneous nodules of different sizes. They are preferentially located on the lower limbs. They have often more erythema and edema around the lesions than the classic erythema nodosum. It is seen in 22.2% of patients in Iran (CI: 1.2). They are seen more frequently in China (8) and Korea (5), around 55% of patients. Other lesions are rare: 1- Erythema Induratum like lesion resembling the erythema induratum of Bazin (33,34). 2- Suppurative panniculitis is a very rare and special subcutaneous form consisting of recurrent episodes of fever with few nodes. These nodes become liquefied followed by the appearance of a fistula draining a sterile liquid. A localized atrophy with a round depressed region is left as sequela. Five cases have been reported from Iran (34).

Ocular Manifestations

They are the major cause of morbidity in BD. Ophthalmological manifestations are seen in 55.6%

of patients in Iran (CI: 1.4), in 69% in Japan, 28.9% in Turkey, 28.5% in Korea, 67% in Morocco, and 68% in England. The low figures from Turkey and Korea may be due to the clinical setting of the centers (Dermatology). Another report from Turkey gives the figure of 47.4% in a Rheumatology setting (35). All parts of the eye may be involved, even conjunctiva and cornea. Anterior uveitis is seen in 41% of patients in Iran (1.4), while posterior uveitis is seen in 44.4% (CI: 1.4), and retinal vasculitis in 30.5% (CI: 1.3) of patients.

Joint Manifestations

They are not rare and seen in 34.3% of patients in Iran (CI: 1.3), in 57% in Japan, 16% in Turkey, 24.2% in Korea, 56.9% in Morocco, and 93% in England. Looking at another statistic from Turkey coming from a rheumatology setting, the figure increases to 46.9% (35). Joint manifestations progress by attacks and remissions. Attacks may last weeks or months. Erosions are exceptional. Attacks may take any form, from arthralgia to arthritis mimicking from an acute and mobile arthritis like rheumatic fever to a chronic, fix, and additive arthritis like rheumatoid arthritis. Arthralgia, of inflammatory type is seen in 15.2% of patients in Iran (CI: 1), 9.8% in Israel (14), 62.4% in Morocco (36), 45% in Lebanon (13), 9.4% in Yorkshire (37), and 16% in Turkey (38). Arthritis is usually mono or oligoarticular. It affects mainly large joints with a predilection for the lower limb, much as the seronegative spondylarthropathies. Polyarticular arthritis, affecting small and large joint, mimicking rheumatoid arthritis is exceptional. Monoarthritis is seen in 7.6% of patients in Iran (CI: 0.7), 20% in Russia (19), 3.4% in India (9), 18% in Lebanon, and 16.2% in Morocco (36). Oligo/poly arthritis is seen in 16.6% of patients in Iran (CI: 1) and 51% in Russia. Oligoarthritis is seen in 34.5% in India, 23% in Lebanon, and in 11.8% in Morocco. Polyarthritis is seen in 32.8% in India, 11% in Lebanon, and in 17% in Morocco. Incidence of ankylosing spondylitis (AS) in BD is controversial. In Iran AS is seen in 1.5% of patients (CI: 0.3), which is 15 times greater than in the general population. In Egypt AS is seen in 5.6% of patients (39), in Iraq in 2% of patients (40), in Lebanon in 1% and in Morocco in 0.83% of patients.

Neurological manifestations

Neuro Behcet (NB) is rare with severe morbidity and seldom mortality. The classic manifestation is a meningoencephalitis. However all forms of neurologic manifestations have been reported: from behavioral problems to organic confusional states, as well as seizures, headache, benign intracranial hypertension, diencephalic dysfunction, aphasia, pseudobulbar palsy, brainstem syndromes, cranial nerve palsies, hemiplegia, cerebellar syndromes, myelopathy, and mononeuritis multiplex may be seen (41-42). NB was seen in 9.5% of patients in Iran (CI: 0.9), in 11% in Japan, in 2.2% in Turkey, in 5.7% in Korea, in 14% in Morocco and in 31% in England (table 1). If headache is set aside, the frequency of NB in Iran decreases to 3.2% (CI: 0.5).

A study from Turkey showed an incidence of 14.2% (headache included) (43). Patients with NB were only 5.3%. In a study from Iran, comparison of patients versus controls showed headache in 37% of BD patients and 43% of controls (42). In BD, headache was of tension type in 57%, vascular type in 28.5%, associated with attacks of mouth ulcers in 12%, and with attacks of uveo-retinitis in 1.5% of BD patients. The difference with the control group was not statistically significant. NB is extremely rare as the initial manifestation of BD, appearing usually several months or years after its onset. Neurological manifestations are essentially due to vasculitis although other causes may be implicated (44). Computed tomography scans are of little help for the diagnosis (43) and show the same images in BD and controls (44). In another study from Turkey, 81% of lesions were parenchymal (hemispheric, brainstem, spinal cord), with pyramidal signs, hemiparesis, behavioral changes, and sphincter disturbance (45). In the others it was dural sinus thrombosis with raised intracranial pressure.

Gastrointestinal (GI) manifestations

They are not rare. Classically they are produced by aphthous ulcers of the intestinal tract, which may be situated on every part of it. GI manifestations are seen in 7.6% of patients in Iran (CI: 0.7), in 15.5% in Japan, in 2.8% in Turkey, in 4% in Korea, and in 7% in England (Table 1).

The classical form of GI manifestations is the ulceration of the ileo-caecal region with symptoms varying from abdominal pain, diarrhea or constipation, proctorrhagia, to acute abdomen due to perforation of ulcers. However, ulcers are not localized only at the 2 extremities of the digestive tract. Ulcers can be seen all along the digestive tract with various clinical symptoms (46).

Dysphagia, retrosternal pain, and hematemesis are due to esophageal ulcers. Gastritis, peptic ulcers, abdominal pain, and diarrhea may be due to stomach and small intestine ulcers. Large intestine may also have ulcers, from the cecum and the ascending, transverse, and descending colon, to sigmoid, rectum and anus. The association of BD and ulcerative colitis has been reported. Gastroduodenitis was seen in 2.7% (CI: 0.4) of patients in Iran, peptic ulcers in 1.5% (CI: 0.3), diarrhea in 2% (CI: 0.4), proctorrhagia in 0.8% (CI: 0.2), and acute abdominal pain in 1.7% (CI: 0.4) of patients. A prospective colonoscopic study of 46 consecutive BD and 27 Rheumatoid Arthritis (RA) patients (47) didn't demonstrate a significantly difference for the occurrence of lower intestinal involvement in them. However, aphthous ulcers were significantly more frequent in BD than in RA (26.1% versus 3.7%).

The main differential diagnosis of lower intestinal lesions is with Crohn's disease. Both have the same ulceration. However colonoscopic study of 94 BD patients with lower intestinal involvement and 67 Crohn's disease showed that ulcers in BD were usually round or oval, while in Crohn's disease they were mainly longitudinal. In case of a longitudinal ulcer, if it has a focal distribution it is mainly BD, otherwise (segmental or diffuse distribution) it is Crohn's disease (48).

Hepatosplenomegaly was rarely seen; only in 25 patients in Iran (0.5%, CI: 0.2).

Vascular involvement

They were seen in 8.5% of cases in Iran (CI: 0.8), in 8.9% in Japan, and in 16.8% in Turkey. They include arterial and venous involvement. Arterial involvement includes thrombosis, aneurysms, and pulse weakness. They are rarely seen and all reports are unanimous on its rarity, except for Saudi Arabia with a rate of 18%. In Iran arterial involvement was

seen in 0.5% of patients (CI: 0.2). Arterial thrombosis was seen in 4 patients, aneurysm in 25 patients, and pulse weakness in 2 patients. Deep vein thrombosis (DVT) is the main feature. It was seen in 8.2% of patients in Iran (CI: 0.8), in 8.9% in Japan, in 10.6% in Turkey, in 19.2% in Morocco, and in 22% in England. Symptoms and the outcome are the same as for phlebitis of other origin, but with more tendency to recur. Superficial phlebitis, although rare, is one of the characteristics of BD. It is segmental, appearing as a subcutaneous longitudinal swelling. It is transient, disappearing in a few days. It was seen in 2.3% of patients in Iran (CI: 0.4). Large vein thrombosis involves mainly superior and inferior vena cava, but may also involve mesenteric, portal, hepatic, splenic, iliac, femoral, subclavian, and axillary veins. It was seen in 1% of patients in the Iran (CI: 0.3). In one study, systematic evaluation of patients with high resolution color duplex sonography showed 79% vascular involvement (63% arterial involvement, 55% venous manifestations, and 39% both). Major arterial lesions were present in 33% and minor lesions in 48% of patients (49).

Pulmonary manifestations

These manifestations have different etiology; vasculitis, embolism, fibrosis, pleurisy, and infection. Although rare, pulmonary manifestations were the leading cause of death in BD, especially pulmonary vasculitis. Forty one cases (0.8%) were seen in Iran survey (CI: 0.2). Vasculitis was seen in 10 patients, fibrosis in 3 patients, embolism in 6 patients, pleurisy in 6 patients, infection in 17 patients, and other lesions in 9 patients.

Cardiac manifestations

They are as rare as pulmonary manifestations. They were seen in only 26 cases in Iran (0.5%, CI: 0.2). Angina pectoris was seen in 6 cases, myocardial infarction in 4 cases, murmur in 7 cases, heart failure one case, and pericarditis in 6 cases. Multiple case reports can be found in the literature on cardiac manifestations describing every form of cardiac involvement.

A study on 30 cases of BD and 30 control patients (50) showed a higher incidence of mitral valve prolapse (50%) and proximal aorta dilatation

(30%) in BD patients than in controls (6.6% and 0%). The difference was statistically significant. In another study 104 BD and 144 control patients were studied in a double blind case control study (51). There was no statistically significant difference between cardiac symptoms and signs, EKG abnormalities, chest x-ray, and echocardiography.

Orchitis, Epididymitis

They were seen in 5.6% of male patients in Iran (CI: 0.6), and 6% in Japan.

They were seen with much higher incidence (up to 28%) in some reports (table 1). They have a low tendency for recurrence. The attack of epididymitis may be a painful or a painless swelling, lasting few days or weeks. The attack of orchitis is painful and affects both testicles.

Renal Manifestations

Urinary abnormalities are not frequent, and are usually transient. They were seen in 10.4% of cases in Iran (CI: 0.9). Proteinuria was seen in 2.2% (CI: 0.4), hematuria in 4.8% (CI: 0.6), leukocyturia in 5.4% (CI: 0.6), and cast in 0.3% (CI: 0.2) of cases. In 14 patients urinary abnormalities became chronic necessitating kidney biopsy. WHO type II was found in 3 cases, type III in 5 cases, type IV in 5 cases, and amyloidosis in 2 cases. Amyloidosis has been reported with much higher frequency from Turkey (52, 53). Since amyloidosis is exceptional in Japan and Iran, and considering that amyloidosis is very frequent as an inherited disease in Turkey, it may be concluded that the Turkish cases of BD and amyloidosis may be a fortuitous association of the two. A case of renal transplant for an end stage WHO type IV glomerulonephritis was reported with a successful outcome at 28 months after the transplantation (54).

Overlap

An association with another disease may be seen. It may be difficult to find a relationship between the two entities. The association may be just fortuitous. An overlap or association was seen in 79 patients in Iran (1.6%, CI: 0.3).

LABORATORY FINDINGS

Erythrocyte Sedimentation rate (ESR) was normal in 46.6% of cases in Iran (CI: 1.4). ESR from 20 to 50 mm was seen in 36% (CI: 1.4), between 50 and 100mm in 15.8% (CI: 1), and superior to 100 mm in 1.6% (CI: 0.4) of patients. Pathergy test was discussed in skin manifestations, and urinary abnormalities in renal manifestations section.

DISEASE CLASSIFICATION

The percentage of patients in Iran, classified by different sets of diagnosis criteria were: Mason & Barnes criteria 67.5% (CI: 1.3), O'Duffy criteria 71.5% (CI: 1.2), International criteria 81.8% (1.1), Dilsen criteria 85.8% (CI: 1), Japan criteria 87.4% (CI: 0.9), Iran criteria (traditional format) 92.5% (CI: 0.7), and the Classification Tree 97.3% (CI: 0.4). Classification Tree (Fig. 1) has the best accuracy among other diagnosis criteria (55).

The accuracy of the International criteria was low. A recent study performed in China, in Iran, and in Korea on a standardized protocol confirmed the low sensitivity and the low accuracy of the International criteria versus the Classification Tree (56). The same was demonstrated in Russia (57), USA (58), Singapore, and India (59).

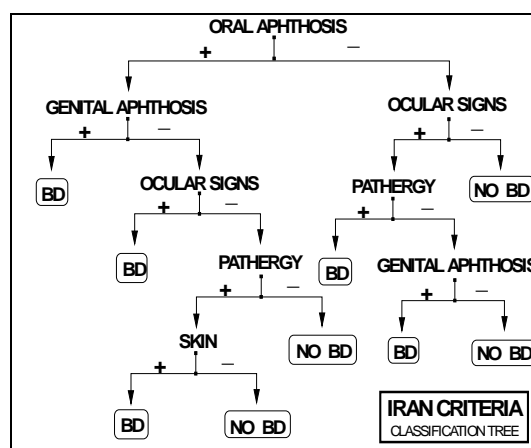


Fig. 1. Classification tree for diagnosis of Behçet's disease based on Iran criteria.

CONCLUSION

The comparison between Japan and Iran surveys demonstrates some differences: In Japan survey there was a higher incidence for genital aphthosis (+8%), skin manifestations (+15%), ocular symptoms (+13%), joint manifestations (+21%), G.I. manifestations (+8%), and neurological manifestations (+8%). The difference may be due to differences in patients' selection, although racial differences cannot be ruled out. In Japan survey the patients' selection was done by questionnaires sent to randomly selected hospitals and the diagnosis was based on Japan criteria. This kind of selection may discard milder forms of the disease, increasing subsequently the percentage of all symptoms. For the Iran study all diagnosed patients all over Iran were included in the study and the diagnosis was not limited to a specific diagnosis criteria. The selection method in Iran permits the inclusion of milder forms of Behçet's Disease. An analysis of BD in Turkey, Iran, Tunisia, Japan, and Korea led Dilsen (60) to the same conclusion (methodological, genetic and environmental factors).

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