LARGE VESSEL INVOLVEMENT IN BEHCET'S DISEASE

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Abstract- Large vessel involvement is one of the hallmarks of Behcet's disease (BD) but its prevalence varies widely due to ethnic variation or environmental factors. The aim of this study is to find the characteristics of vasculo-Behcet (VB) in Iran. In a cohort of 4769 patients with BD, those with vascular involvement were selected. Different manifestations of disease were compared with the remaining group of patients. A confidence interval at 95% (CI) was calculated for each item. Vascular involvement was seen in 409 cases (8.6%; CI, 0.8). Venous involvement was seen in 396 cases, deep vein thrombosis in 294 (6.2%; CI, 0.7), superficial phlebitis in 108 (2.3%; CI, 0.4) and large vein thrombosis in 45 (0.9%; CI, 0.3). Arterial involvement was seen in 28 patients (25 aneurysms and 4 thromboses). Thirteen patients showed both arterial and venous involvement. The mean age of the patients with VB was slightly higher (P<0.03), but the disease duration was significantly longer (P<0.0003). VB was more common in men. As the presenting sign, ocular lesions were less frequent in VB (P<0.0006), while skin lesions were over 2 times more common in these cases (P<0.000001). VB was associated with a higher frequency of genital aphthosis, skin involvement, joint manifestations, epididymitis, CNS lesions and GI involvement. The juvenile form was less common in VB (P<0.03). High ESR was more frequent in VB (P=0.000002), but the frequency of false positive VDRL, pathergy phenomenon, HLA-B5 or HLA-B27 showed no significant difference between the two groups. In Iranian patients with BD, vascular involvement is not common and large vessel involvement is rare. It may be sex-related, and is more common in well-established disease with multiple organ involvement and longer disease duration.

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INTRODUCTION

Behcet's disease (BD) is a multi-system disease characterized mainly by recurrent oral and genital ulcers, skin and ocular lesions. It spares no organ in the body, and other organs involvement occur as minor manifestations of the disease (1). Vascular involvement, as a hallmark of BD, involves arteries and veins of all sizes (2).

It may be a poor prognostic sign, especially when involving major vessels (3). Like the other manifestations of disease, its prevalence varies widely according to reports from different parts of the world (1.8 to 79%) (3-22). The difference may be due to ethnic variation or environmental factors (1). Here we present the prevalence and characteristics of vascular lesions in Iranian patients with BD, and the possible effect of these lesions on disease expression.

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MATERIALS AND METHODS

In a cohort of 4769 patients with the diagnosis of BD, registered at our BD unit during the past 27 years (between 1975 and March 2002), those with vascular involvement were selected. The confirmatory diagnostic procedures for venous thrombosis were either doppler sonography or phlebography, and for arterial involvement were

either angiography or computerized tomography (CT) scanning. The remaining patients without vascular lesions were assigned as control group (non VB).

A computerized form including 100 clinical and paraclinical parameters was used to register different manifestations of the disease. These data were compared between the two groups by chi square test and corrected by Fisher exact test. Standard deviation for the means (SD), their related standard error of means (SEM), and a confidence interval at 95% (CI) were calculated for each item.

RESULTS

Vascular involvement was seen in 409 cases (8.6%, CI=0.8). The control group included 4360 BD patients. The mean age of the patients was 27 years (SD=9.2, SEM=0.455), slightly higher than the control group (25.9±9.7 years, SEM=0.147) but statistically significant (P<0.03). VB was more common in men (77%±4.1 versus 52%±1.5, P<0.000001), with male/female ratio of 3.4, and the mean disease duration was significantly longer in men (10.4±7.5 versus 9.1±6.9 years, P<0.0003). The mean follow-up time for VB patients was also longer (4.1±4.6 versus 2.8±3.7 years, P<0.000001).

Venous involvement was seen more frequently (396 cases, 8.3%, CI=0.8). They included deep vein thrombosis (DVT) in 294 (6.2%, CI=0.7), superficial phlebitis in 108 (2.3%, CI=0.4), and large vein thrombosis in 45 (0.9%, CI=0.3). In the latter group with large vein thrombosis, the involved vein was superior vena cava in 19 patients, inferior vena cava in 9 and iliofemoral in 10 cases.Brachiocephalic and subclavian veins occlusion were seen each in 1 case. Three patients presented with Budd-Chiari syndrome due to suprahepatic vein occlusion. Two patients presented with portal hypertension, and another one with splenomegaly due to splenic vein thrombosis. We have seen 2 cases of cerebral sinus occlusion and a case of jugular vein thrombosis.

Arterial involvement was seen in 28 patients (0.6%, CI=0.2). Aneurysms were present in 25 patients and thrombosis in 4. In the case of arterial aneurysms, the following arteries were involved: aorta in 9 cases, iliac and femoral artery each in 5 cases, popliteal in 3 cases, posterior tibialis in 2 cases, subclavian, pulmonary and cerebral arteries each in one case. In the 4 cases of arterial thrombosis, the involved arteries were iliac, aorta, and popliteal arteries (2 cases). We encountered 3 cases with pulse weakness, 2 in the radial and 1 in the femoral artery, without any evident arterial thrombosis or aneurysm.

Thirteen patients showed involvement of both arterial and venous systems. The arterial involvement was aneurysmal in all, but thrombosis was also present in 2 of them. The venous involvement was DVT in 8 cases (accompanied by larger vein involvement in 2 cases, and by superficial phlebitis in another one), superficial phlebitis in 5 cases (one with DVT), and large venous involvement in 3 cases (two with DVT). Comparison between the groups with and without vascular involvement showed no significant difference in the presence of positive familial history of BD (4.2%, CI=2.8 versus 5.3%, CI=0.9, P=0.4), or oral aphthosis (47.4%, CI=7.1 versus 50.2%, CI=2.1, P=0.46). But the prevalence of juvenile form of the disease was significantly lower in those with vascular involvement (2.4%, CI=1.5 versus 4.9%, CI=0.6, with P<0.03). As the presenting sign, ocular lesions were less frequently seen in VB (4.9%, CI=2.1 versus 10.2%, CI=0.9, P<0.0006) and the frequencies of oral and genital aphthosis, and joint manifestations were the same (Table 1). Other manifestations of the disease, notably skin lesions, were over 2 times more common in VB as the first manifestation of the disease (15.9%, CI=3.6 versus 7.4%, CI=0.8, P<0.000001). VB was associated with a higher frequency of genital aphthosis (73.3%, CI=4.3 versus 64.5%, CI=1.4, P<0.0004) and skin involvement (88%, CI=3.1 versus 68.5%, CI=1.4, P<0.000001). It was very prominent in the case of erythema nodosum (50.6%, CI=4.8 versus 19.6%, CI=1.2, P<0.000001). The frequencies of other major symptoms were nearly the same (Table 2). All the minor manifestations of disease, including joint manifestations (53.8%, CI=4.8 versus 33%, CI=1.4, with P<0.000001), gastrointestinal involvement (11.7%, CI=3.1 versus 7.5%, CI=0.8, P<0.003), CNS lesions (6.8%, CI=2.5 versus 2.9%, CI=0.5, P<0.00002), and epididymitis (21%, CI=4.5 versus 9.1%, CI=1.2, P<0.000001) were more frequent in patients with vascular involvement (Table 3).

Table 1. Comparison between presenting signs of vascular and non-vascular groups

Presenting sign	Vascular % (CI)	Non-vascular % (CI)	*P* value
Oral aphthosis	77.8 (4)	80.6 (1.2)	0.17
Genital aphthosis	9.8 (2.9)	10.4 (0.9)	0.69
Ocular lesions	4.9 (2.1)	10.2 (0.9)	<0.0006
Joint manifestations	6.8 (2.5)	5.1 (0.6)	0.13
Other involvement	15.9 (3.6)	7.4 (0.8)	<0.000001

Abbreviation: CI, confidence interval.

In laboratory findings, high ESR was more frequent in VB (65.4%, CI=4.8 versus 52.8%, CI=1.5, with *P*=0.000002). The frequency of other paraclinical tests such as pathergy phenomenon, urine abnormality, false positive VDRL, HLA-B5 or HLA-B27 showed no significant difference between the two groups (Table 4).

DISCUSSION

Large vessel involvement in BD can take the form of venous thrombosis, arterial occlusions, and arterial aneurysms (2,3,23). Due to their low sensitivity, vascular lesions are not listed among the criteria for diagnosis of BD in most major sets of diagnostic criteria (1,2,23). However they may be distinctive and should suggest the diagnosis of BD when present

Table 2. Comparison between major manifestations of vascular and non-vascular groups

Major manifestation	Vascular % (CI)	Non-vascular % (CI)	*P* value
Oral aphthosis	98.3 (1.4)	96.5 (0.5)	0.07
Genital aphthosis	73.3 (4.3)	64.5 (1.4)	<0.0004
Skin lesions	88 (3.1)	68.5 (1.4)	<0.000001
Pseudofolliculitis	70.9 (4.4)	60.9 (1.4)	0.00007
Erythema nodosum	50.6 (4.8)	19.6 (1.2)	<0.000001
Ocular lesions	51.6 (4.8)	56.2 (1.5)	0.07

Abbreviation: CI, confidence interval.

Table 3. Comparison between minor manifestations of vascular and non-vascular groups

Minor manifestation	Vascular % (CI)	Non-vascular % (CI)	*P* value
Joint manifestations	53.8 (4.8)	33 (1.4)	<0.000001
GI involvement	11.7 (3.1)	7.5 (0.8)	<0.003
CNS involvement	6.8 (2.5)	2.9 (0.5)	<0.00002
Epididymitis (men)	21 (4.5)	9.1 (1.2)	<0.000001

Abbreviation: CI, confidence interval.

(23).

Among the connective tissue diseases, BD surpasses SLE as a cause of venous occlusive disease (2). According to the literature, the most common vascular lesions are subcutaneous thrombophlebitis and venous occlusion of the upper and lower extremities (3). Thrombosis may be recurrent and may also affect the vena cava, the cerebral venous sinuses and the portal venous system, leading to characteristic clinical syndromes. Although superficial and deep venous thrombosis is associated with a higher risk of thrombosis in other locations as well as arterial lesions (3,23), pulmonary emboli are rare and the role of anticoagulant therapy is uncertain (2).

Arterial involvement includes aneurysm formation (in about two thirds of cases and often multiple), thrombosis, and angiitis of systemic and pulmonary arteries.

Table 4. Comparison between laboratory findings of vascular and non-vascular groups

Laboratory finding	Vascular % (CI)	Non-vascular % (CI)	*P* value
Positive pathergy test	60.8 (4.8)	57.7 (1.5)	0.23
High ESR	65.4 (4.8)	52.8 (1.5)	0.000002
Urine abnormality	9.6 (3)	10.9 (1)	0.42
False positive VDRL	2.4 (1.6)	1.6 (0.4)	0.38
HLA-B5	54.3 (5)	53 (1.5)	0.62
HLA-B27	8 (3)	9.4 (0.9)	0.41

Abbreviation: CI, confidence interval.

The artery most often affected is the aorta, followed by the pulmonary, femoral, popliteal, subclavian and common carotid arteries. Based on isolated reports, virtually no arteries are spared, including the coronary arteries. Isolated arterial stenoses and occlusions are the least common vascular complications but arterial occlusions are often associated with aneurysms (2).

BD is one of the known acquired disorders that lead to the formation of pulmonary artery aneurysm. These patients can present with asymptomatic abnormalities on chest radiographs, but massive and fatal hemoptysis from ruptured pulmonary artery aneurysms and arteriobronchial fistula may be the unsuspected manifestations of BD. Rupture of these large artery aneurysms is one of the leading causes of death in patients with BD (2). It would be interesting to compare our data with various reports from the other parts of the world (Table 5). In Iranian patients with BD, vascular involvement is not common and large vessel involvement is rare. Similar prevalence is seen in large series, such as Iran and Japan (4), with nationwide surveys. The higher reported frequencies may be in part due to bias of small series or hospital-based selection of the patients, as well as ethnic variations. Vascular lesions were more common in men, and in those with well-established disease, with multiple organ involvement and longer disease duration. The mean time for the emergence of vascular lesions from the time of diagnosis was reported 3.2 years in Turkish patients (3). Recently, we have reported a mean delay time of 6.5 years after the onset of the disease for the appearance of vascular lesions in Iranian patients with BD (24). There is a large difference between our BD patients with and without vascular involvement in different manifest-tations of the disease. Higher frequency of genital aphthosis, skin lesions, epididymitis, joint, gastroin-testinal, and CNS involvement, as well as high ESR was seen in VB patients (Tables 2 and 3). No relationship seems to exist between vascular involvement and HLA-B5 genetic background, as well as false positive VDRL or pathergy phenomenon in our BD patients (Table 4).

Table 5. Frequency of vascular involvement in different parts of the world*

	Number of patients	Vascular involvement	Venous involvement†	Arterial involvement	Superficial phlebitis
Iran (Shahram)	4769	8.6	7	0.6	2.3
Japan (Nakae[4])	3316	8.9			
Korea (Bang[5])	1527	1.8			
China (Dong Yi[6])	120	12.5	7.5	5	2.5
S.Arabia (Al-Dalaan[7])	208	33	28.4	19.2	
Turkey (Sarica[8])	2319	14.3	6.1	0.9	9.4
Jordan (Madanat[9])	200		24	3.5	7
Iraq (Sharqui[10])	100	21	5		16
Israel (Krause[11])	91	26.4			
Tunisia (Hamza[12])	515	25	22	4	
Morocco (Benamor[13])	316		21.8		
Egypt (Assaad Khalil[14])	100	79	55	63	40
Algeria (Berrah[15])	58	33	30	6.9	6.9
USA (Calamia[16])	164	19	16.5	4.3	
Portugal (de Jesus[17])	43	28	9.3	4.7	16.3
Italy (Valesini[18])	155	25.1	23.2	1.9	
Russia (Prokaeva[19])	77	18	17	2.4	1.3
Germany (Zouboulis[20])	141	25			15
England (Chamberlain[21])	32		25	3.1	
Greece (Kaklamani[22])	101	11			

*Data are presented as percentage unless otherwise indicated.

†Including deep vein thrombosis and large vein thrombosis.

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