

What is the impact of traditional risk factors for vascular affection on Behcet's disease vascular involvement: a retrospective cohort study

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Received 26 March 2019

Accepted 13 April 2019

Egyptian Rheumatology & Rehabilitation 2019, 46:257–261

Background

To study the frequency, types, and outcome of vascular involvement in a cohort of Egyptian patients with Behcet's disease (BD) and its relation to traditional risk factors for vascular affection.

Patients and methods

A retrospective cohort study was done involving 164 patients with BD diagnosed according to the criteria of the International Study Group for BD admitted to Cairo and Ain Shams Universities Hospitals from 2000 to 2017. They were reviewed to analyze the types, risk factors, and outcome of vascular involvement.

Results

A total of 148 men and 16 women were included in the study, with a mean age of 31.5±7.5 years. Their disease duration ranged from 1 to 36 years, with a mean of 7.3±5.5 years. Vascular involvement was present in 64 (39%), involving both venous and arterial sides of the circulation. Venous affection was more common than arterial (39 and 17%, respectively). No significant association was found between traditional risk factors for vascular affection (smoking, hypertension, diabetes, hyperlipidemia, and obesity) and vascular involvement in patients with BD. Although uncommon, arterial aneurysm (9.8%) is the most serious complication, as it may lead to mortality owing to aneurysm rupture and bleeding (representing 100% of deaths in this study).

Conclusion

Vascular involvement in patients with BD is mainly owing to the disease process itself and not owing to the effect of the traditional risk factors for vascular affection, reflecting the importance of focusing on treatment of the disease process. However, adjustment of these risk factors would lead to better health outcome for the vulnerable patients.

Keywords:

Behcet's disease, risk factors, vascular outcome, vasculitis

Egypt Rheumatol Rehabil 46:257–261

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1110-161X

Background

Behcet's disease (BD) is a nonspecific vasculitis involving both veins and arteries [1]. It may cause vasculitis of all types of blood vessels. Vascular involvement is a well-known complication of BD, involves up to 40% of patients, and is considered a poor prognostic factor in BD [2].

Venous disease resulting in venous thrombosis is more frequent than arterial affection and is usually an early feature of BD. Superficial and deep vein thrombosis (DVT) can occur in addition to the less common superior and inferior vena cava occlusion, Budd–Chiari syndrome, dural sinus thrombosis, and other venous obstructive lesions [3]. DVT of legs is usually the first vascular event of patients with BD and the most common localization [4].

Arterial system involvement is uncommon and may be in the form of aneurysm formation in two-thirds of

arterial involvement cases and occlusive arteritis in the remaining one-third [1]. The inflammatory process at arterial vessels usually leads to aneurysms owing to acute and destructive vasculitis [5]. Peripheral arteries are more commonly affected in BD [6]. The most commonly involved arteries are carotid, pulmonary, aortic, iliac, femoral, and popliteal; however, cerebral and renal arteries are less commonly involved [7]. Owing to coronary artery vasculitis, acute myocardial infarction can occur in patients with BD, but it is uncommon [8]. Pulmonary artery aneurysms are characteristic of BD and have a poor prognosis [9]. The unique pulmonary vascular lesion in BD is the affection of large proximal

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branches of the pulmonary artery, which are uncommonly seen in diseases other than BD [10].

Although the classic pathological BD's lesion is necrotizing leukocytoclastic obliterative perivasculitis and venous thrombosis with lymphocytic infiltration of capillaries, veins, and arteries of all sizes [11], we decided to study the effect of the major modifiable risk factors for vascular diseases in general [12]: high blood pressure, dyslipidemia, smoking, and diabetes mellitus on vascular involvement in patients with BD.

Many studies were performed on Egyptian patients with BD but did not focus on vascular affection in these patients, its types, and outcome. Moreover, to our knowledge, no studies have focused on the effect of traditional risk factors for vascular affection on patients with BD with vascular involvement. So, the aim of the present study was to assess these points by studying the frequency, types, and outcome of vascular involvement in these patients and its relation to traditional risk factors for vascular affection.

Patients and methods

The medical records of 164 patients with BD who were admitted and followed up in Cairo and Ain Shams Universities Hospitals between 2000 and 2017 were retrospectively reviewed to analyze the frequency, types, and outcome of vascular involvement. Of 164 patients with BD, four died, and they were included in this study.

Diagnosis of BD was made according to the criteria of the International Study Group for BD [13].

The collected data included the following: (a) basic demographic characteristics (age, sex, age of onset, and disease duration); (b) clinical manifestations, where in our study, we focused on the vascular affection in BD in addition to associated other systems affection; (c) the laboratory investigations including complete blood picture, erythrocyte sedimentation rate (ESR), liver and kidney function tests in addition to lipid profile and fasting blood sugar, (d) the major modifiable risk factors for vascular involvement (obesity, smoking, diabetes, hypertension, and hyperlipidemia) [14], and (e) medical treatment for BD.

Statistical analysis

An IBM-compatible PC was used to store and analyze the data. Calculations were done by means of statistically software package, namely, 'SPSS 13' for Windows (SPSS Inc., Chicago, Illinois, USA). Results

were expressed as mean±SD. χ^2 -Test was used for qualitative data. Values were considered statistically significant if *P* value is equal to or less than 0.05. Logistic regression analysis was done to test for significant predictors of vascular affection.

Ethical approval and consent

The study was approved by the Local Ethics Committee of Cairo University and Ain Shams Scientific Review Board, and informed consent was obtained from all patients according to the 2008 Declaration of Helsinki.

Results

Demographic data and laboratory investigations of the patients are shown in Table 1 and clinical manifestations in Table 2. The most common clinical combination was vascular and ocular involvement which occurred in 60% of the patients. Numbers and percentage of different forms of vascular affection of the patients are shown in Table 3. Association between vascular involvement and traditional risk factors for vascular affection (obesity, hyperlipidemia, smoking, diabetes, and hypertension) was shown in Table 4. No significant association was found. Also, logistic regression analysis was done to

Table 1 Demographic data and laboratory investigations of the Egyptian patients with Behçet's disease

Demographic data in patients with BD (n=164)	
Age (years)	31.5±7.5 (17–52)
Sex (male : female)	148 : 16 (9.25 : 1)
Smokers	54 (34.1)
Age at onset (years)	29.7±5.2 (15–48)
Disease duration (years)	7.3±5.5 (1–36)
ESR (mm/first hour)	25.5±19.2
Hemoglobin (g/dl)	12.3±2.4
Platelets ($\times 10^3/\text{mm}^3$)	245.3±79.5
TLC ($\times 10^3/\text{mm}^3$)	7.3±1.5
AST (U/l)	24.4±11.6
ALT (U/l)	29.6±20.7
Creatinine (mg/dl)	0.78±0.24
Urea (mg/dl)	18.7±4.3

ALT, alanine transaminase; AST, aspartate transaminase; BD, Behçet's disease; ESR, erythrocyte sedimentation rate; TLC, total leukocyte count.

Table 2 Main clinical manifestations of Egyptian patients with Behçet's disease presented as percentage from total number of patients

Clinical manifestations	n (%)
Mucocutaneous	164 (100)
Ocular	99 (60.3)
Vascular	64 (39)
Neurological (parenchymal)	17 (10.3)

Table 3 Percentage of different forms of vascular affection in Egyptian patients with Behçet's disease

Clinical manifestation	No. of patients	Percentage (%) from total number of patients
A) Venous involvement:	64	39
1- Lower extremities DVT	46	28
2- Sigmoid sinus thrombosis	2	1.2
3- Transverse sinus thrombosis	4	2.4
4- Superior sagittal sinus thrombosis	4	2.4
5- Superior vena cava thrombosis	2	1.2
6- Inferior vena cava thrombosis	4	2.4
B) Arterial involvement:	28	17
1- Aneurysm	16	9.8
2- Brain vasculitis	12	7.3

Table 4 Association between vascular involvement in patients with Behçet's disease and known risk factors of vascular affection

Risk factors	Vascular affection		Non-Vascular affection		X ²	P value
	NO.	%	NO.	%		
Smoking						
Present	26	40.6	30	30	1.959	0.161
Absent	38	59.4	70	70		
Hypertension						
Present	12	18.75	15	15	0.399	0.527
Absent	52	81.25	85	85		
Diabetes Mellitus						
Present	5	7.8	9	9	0.070	0.790
Absent	59	92.2	91	91		
Obesity						
Present	10	15.6	7	7	3.124	0.077
Absent	54	84.4	93	93		
Hyperlipidemia						
Present	33	51.5	61	61	1.420	0.233
Absent	31	48.5	39	39		

Table 5 Logistic regression analysis for significant predictors of vascular affection in patients with Behçet's disease

a	P value	OR	95% CI for OR	
			Lower	Upper
Hypertension	0.851	0.852	0.160	4.529
Diabetes	0.617	0.578	0.068	4.948
Smoking	0.464	1.539	0.485	4.887
Obesity	0.063	9.062	0.890	92.275
Hyperlipidemia	0.373	0.609	0.205	1.812
Constant	0.260	1.703		

CI, confidence interval; OR, odd ratio. ^aVariable(s) entered on step 1: hypertension, diabetes, smoking, obesity, hyperlipidemia.

test for significant predictors of vascular affection shown in Table 5 and no significance was found.

Table 6 Outcome of vascular involvement in Egyptian patients with Behçet's disease

Outcome	n (%)
Surgical removal of aneurysm	4 (2.4) (25% of cases with aneurysm)
Rupture of aneurysm (living patients)	2 (1.2) (12.5% of cases with aneurysm)
Pulmonary embolism	18 (18.4)
Stroke	14 (8.5)
Death	11 (2.4) (due to aneurysm rupture)

The outcome of patients with vascular affection was shown in Table 6.

Almost all patients ($n=157$; 95.7%) were on steroids at a mean dose of 20.25 ± 9.6 mg/day. The following medications were received by the patients: cyclophosphamide ($n=90$; 54.9%), azathioprine ($n=80$; 48.8%), cyclosporine A ($n=30$; 18.3%), colchicine ($n=40$; 24.4%), biologic therapy ($n=18$ on infliximab and three on adalimumab; 12.8%), methotrexate ($n=10$; 6%), sulfasalazine ($n=3$; 1.8%), and mycophenolate mofetil (one patient). Oral anticoagulants were received by 60 (36.6%) patients.

Discussion

This study was conducted to analyze the vascular manifestations of patients with BD, its clinical outcome and its relation to traditional risk factors for vascular affection.

Our results showed a male to female ratio of 9.25 : 1 (90.2% males and 9.8% females). Sex distribution in patients with BD markedly differs regarding their ethnic origin and residence [14].

Regarding patients with BD in our study, they presented four main clinical subsets including mucocutaneous (100%), ocular (60.3%), vascular (39%) and neurological (10.3%). In another study, all patients had mucocutaneous lesions (100%), eye lesions were present in 64.5%, and neurological involvement in 19% of cases [15].

According to different studies, vascular affection varies widely from 7 to 46% of patients with BD [16]. In this study, it was present in 39%. Similar results were reported in Saudi Arabia and in Turkey [8,17], as the prevalence was 40%. Other reports revealed that vascular involvement was seen 36.8% of cases in Lebanon [18], 20% in Morocco, 7.7% in China, 13% in Germany, 32% in the UK, 10% in the USA, 8.9% in Iran as well as Japan, and 1.8% in Korea [19].

Venous affection is the most frequent form of vascular involvement [2]. This was in agreement with our study, as venous affection was more common than arterial involvement (39 and 17%, respectively). In this work we didn't find isolated arterial affection. Although venous thrombosis occurs mainly in the lower extremities, it may involve many different sites including the inferior and superior vena cava, pulmonary artery, suprahepatic vessels, and cardiac cavities [2]. Davatchi *et al.* [19] mentioned that DVT occurs in 5-22% of patients with BD. However, we reported a slightly higher incidence of lower extremities DVT (28%); this was similar to a Turkish study with DVT reported in 29.8% [20]. However, it was seen in 6.2% of patients in Iran, 8.9% in Japan, 5.3% in China, 16% in Morocco, and 22% in the UK [19]. Superior vena cava thrombosis and inferior vena cava thrombosis have been reported at 9 and 2.5%, respectively [21]. In this study, superior vena cava thrombosis was found in two (1.2%) patients and inferior vena cava thrombosis was found in four (2.4%) patients. In another study, inferior vena cava thrombosis was found 2% of patients and no reported cases for superior vena cava thrombosis [3]. Moreover, another study reported that superior vena cava thrombosis was present in 2.6% of patients and no reported cases of inferior vena cava thrombosis [1].

In this study, arterial aneurysms were found in 9.8%, stroke in 8.5%, sigmoid sinus thrombosis in 1.2%, transverse sinus thrombosis in 2.4%, superior sagittal thrombosis in 2.4% and brain vasculitis in 7.3% of patients. In addition, we found that pulmonary embolism was found in 11%. A similar study reported that pulmonary embolism was found in 12.5% of patients [22]. In this study, arterial involvement was found in 17% which was in harmony with what was reported in Saudi Arabia in 18% [23]. However, in Iran, it was 0.6%, in China 4%, in Morocco 2.5%, in Russia 2.9%, in Turkey 2.6%, in Italy 1.9%, and in Yorkshire 3.1% [19].

Vascular involvement occurs more commonly in patients with BD with ocular affection [1]. This was in agreement with our study in which we found that the most common combination was vascular and ocular involvement, which occurred in 60% of patients with BD.

Concerning outcome of vascular involvement, four (2.4%) patients died owing to a vascular cause (rupture of an aneurysm). In addition, rupture of an aneurysm occurred in the two living patients with vascular involvement and surgical removal of an aneurysm was seen in 6.6% of living patients with vascular disease.

We analyzed the association between vascular involvement in Egyptian patients with BD and traditional risk factors for vascular affection (obesity, hyperlipidemia, smoking, diabetes, and hypertension), and there was no significant association found between them. Moreover, logistic regression analysis was done, and no significant predictors for vascular affection among the traditional risk factors of vascular affection were found. These data prove that vascular affection in patients with BD is owing to vascular inflammation due to the disease process itself rather than any other risk factors. The vascular thrombosis in BD is accepted to be the consequence of vessel wall inflammation, and therefore, the European League against Rheumatism recommendations suggest the use of immunosuppressive drugs in the treatment [24]. In this study, the finding that the traditional risk factors have no effect as a predisposing factor of vascular affection may be related to the patients' age as they have a younger age (the mean age was 31.5 ± 7.5) than those having vascular disease owing to dyslipidemia, hypertension, obesity and smoking, as these factors exert their deleterious effect on the vascular tree through a long disease duration in an older age group.

Conclusion

Vascular involvement in patients with BD is mainly owing to the disease process itself and not owing to the effect of the traditional risk factors for vascular affection, reflecting the importance of focusing on treatment of the disease process. However, adjustment of these risk factors would lead to better health outcome for the vulnerable patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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