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Deep Venous Thrombosis in Behçet's Disease: A Retrospective Study of 430 Tunisian Patients

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Introduction

Behçet's disease (BD) is a chronic inflammatory disorder characterized by an association of recurrent oral aphthae and other manifestations such us genital ulcers, skin lesions, arthritis, uveitis and thrombophlebitis. It may also involve central nervous and gastrointestinal systems [1,2]. The etiology and pathogenesis of BD are not clear, but are presumed to be multifactorial, implicating genetic, infectious and immunologic factors. The predominant histopathological feature in BD is vasculitis with singular properties among other systemic vasculitis manifestations, as it can involves all veins, arteries and vessels of all sizes [3]. The prevalence of vascular involvement in BD varies from 6 to 40% according to the studied population [4,5]; deep venous thrombosis (DVT) are the most frequent vascular manifestation, seen in 6.2 to 33 % cases of BD [5-7]. Pathogenesis of vasculo-BD is still not well established, but it seems that vascular endothelial lesion is the major factor [8].

There are ethnic and regional differences in BD presentation, not only the frequency but also the type of organ lesions seems to differ between regions. These differences could be related to genetic and environmental influences.

DVT are frequent in Tunisian patients with BD [9] and can reveal the disease. Therefore, we carried out this study to determine demographic, clinical and genetic features of DVT in BD through a study of a homogenous group of patients observed in the same department; and to compare them with those of other ethnic and geographic groups.

Patients and Methods

We performed a retrospective review of the records of 430 patients diagnosed as BD in the department of internal medicine, La Rabta University Hospital in Tunis, Tunisia (a tertiary referral centre), over a 20 years period. Diagnosis of BD was made according to the criteria of the International Study Group (ISG) for BD [10]. Patients' files included were analysed for age, sex, presentation, diagnostic criteria, investigations, complications and treatment. The onset of BD was defined as the time when the first symptoms attributed to the disease occurred.

Patients were then divided into 2 groups according to the presence (DVT+) or not (DVT-) of DVT. Patients with superficial thrombophlebitis were excluded.

The diagnosis of DVT was made using venous ultrasonography or computed tomography in cases of vena cava thrombosis or pulmonary embolism. Diagnosis of cerebral venous thrombosis was made using cerebral magnetic resonance imaging (MRI) angiography.

Statistical analysis

Our data were recorded and analysed using the Statistical Package for the Social Sciences (version 11). Data have been expressed as means +/- ranges. Continuous variables were analysed using the Student t-test. Association between the different clinical manifestations in BD patients, were investigated using the Pearson's corrected chi-square test. A value of $p<0.05$ was regarded as statistically significant.

Results:

Four hundred thirty records of patients with BD were analyzed. The patients were native from all parts of Tunisia, they were 295 men and 135 women (sex ratio M/F=2.2). The mean age at the onset of the disease and at BD diagnosis was respectively 29.12 ± 10.24 years and 33.9 ± 10.27 years. The average delay between the first sign of BD and diagnosis was 4.58 ± 5.48 years.

The cumulative frequencies of clinical features in the 430 patients are shown in Table 1. One hundred fifty (34.9%) patients had vascular involvement (venous thrombosis and arterial lesions).

Manifestation	No. of patients (%) n = 430
Oral ulcers	430 (100)
Genital ulcers	341 (79.5)
Pseudofolliculitis	320 (74.4)
Erythema nodosa	73 (17)
Positive pathergy test	177/306 (57.8)
Arthritis/Arthralgia	195 (45.7)
Ocular involvement	200 (46.5)
Neurological involvement	121 (28.1)
Vascular involvement	150 (34.9)
Deep vein thrombosis	119 (27.4)
Arterial aneurysms	23 (5.3)
Arterial thrombosis	6 (1.4)
Intestinal involvement	7 (1.6)

Frequency of HLA B51	84/178 (47.2)

Table 1: Cumulative frequencies of clinical involvements of BD during the disease course.

One hundred and nineteen patients (27.6%) had DVT: they were 98 men and 21 women. The mean age at the onset of BD was 29.88 ± 9.37 years and at the BD diagnosis was 34.33 ±9.86 years. The mean delay to BD diagnosis in this group was 4.01 ± 4.56 years. The average delay between the first sign of the disease and the DVT occurrence was 4.32 ± 5.51 years.

DVT revealed the disease in 65 cases (15%) and was the first sign of BD in 13 patients.

Different locations of DVT were noted (Table 2). The lower extremities were the most frequent location (68%). Twenty nine (24.3%) patients had vena cava thrombosis (VCT); 18 superior vena cava and 16 inferior vena cava thrombosis were noted. Twenty four patients had cerebral vein thrombosis (CVT); nine had pulmonary embolism and patients had six had hepatic vein thrombosis (HVT).

Locations	No of patients (%) n = 119
Lower extremities	81(68)
Upper extremities	1(0.8)
Superior vena cava	18 (15.1)
Inferior vena cava	16 (13.4)
Jugular veins	12 (10)
Hepatic veins	7 (5.8)
Cerebral veins (dural sinus)	24 (20.1)
Pulmonary embolism	9 (7.5)

Table 2: Different locations of deep venous thrombosis in patients with Behçet's disease.

Forty-nine patients (57%) showed more than one location. One hundred fifty five episodes of thrombosis were noted. Recurrence of DVT was noted in 36 patients (30%). DVT was associated to a superficial vein thrombosis in eight patients. Twenty one patients had both venous and arterial lesions (4.8% of BD patients and 17.6 % of patients with DVT).

DVT was significantly more frequent in males (63.3% vs 82.4; $p < 0.0001$).

Comparison between patients with (DVT +) and without DVT (DVT -) (Table 3) showed that genital ulcers and arterial involvement were significantly more frequent in DVT + patients, while ocular involvement were significantly less frequent in this last group.

Demographic, clinical and genetic features	DVT (-) n= 311	DVT (+) n= 119	p
Males n (%)	197 (63.3)	98 (82.4)	< 0.0001
Age (year)	28.82	29.88	NS
Genital ulcer n (%)	239 (77.1)	102 (85.7)	0.04
Pseudofolliculitis n (%)	231 (74.5)	89 (74.8)	NS
Erythema nodosa n (%)	59 (19)	14 (11.8)	NS
Positive pathergy test n (%)	126/222 (56.8)	51/84 (60.7)	NS
Ocular involvement n (%)	161 (51.8)	39 (32.8)	<0.0001
Articular involvement n (%)	151(49)	44 (37)	0.025
Neurological involvement (Non vascular) n (%)	54 (17.4)	30 (25.2)	NS
Arterial involvement n (%)	7 (2.3)	21 (17.6)	<0.0001
Gastrointestinal involvement n (%)	5 (1.6)	2 (1.7)	NS
HLA-B51 (+) n (%)	66/136 (48.5)	18/42 (42.9)	NS
NS = non-significant			

Table 3: Demographic, clinical and genetic characteristics of BD patients with and without deep venous thrombosis throughout BD follow up.

All patients with VCT were male. They were symptomatic; Superior VCT presented with swelling of the face and upper extremities with full jugular veins and thoracic collateral veins. Inferior VCT caused lower extremities edema and prominent venous collaterals in the abdominal wall. Superior VCT was associated to jugular thrombosis in 12 patients. Inferior VCT was associated to lower limbs thrombosis in 13 cases and extended to hepatic veins in 6 patients. There were no differences between patients according to the presence or not of VCT.

Patients with CVT (5.5%) were 15 male and 9 female. The major symptom in these patients was persistent headache (45.8%). Cerebrospinal flow hypertension was noted in all cases when it was measured. Left lateral sinus was the most frequent location (7 cases). The CVT was associated to other venous thrombosis in 10 patients (41.6 %) especially lower limbs thrombosis (8 patients). Comparison between patients with and without CVT (Table 4) showed that arterial involvement were significantly more frequent in patients with CVT, while ocular involvement and HLA-B51 were significantly less frequent in this group of patients.

Demographic, clinical and genetic features	CVT (-) n=406	CVT (+) n=24	p
Genital ulcer n (%)	323 (79.8)	18 (75)	NS
Pseudofolliculitis n (%)	309 (76.3)	11 (45.8)	0.001
Erythema nodosa n (%)	71 (17.5)	2 (8.3)	NS
Positive pathergy test n (%)	163/288 (56.6)	14/18 (77.8)	NS
Ocular involvement n (%)	194 (47.8)	6 (25)	0.03
Articular involvement n (%)	186 (46.2)	9 (37.5)	NS
Neurological involvement (Non vascular) n (%)	75 (18.5)	9 (37.5)	0.032
Vena cava thrombosis n (%)	27 (6.7)	2 (8.3)	NS
Arterial involvement n (%)	20 (4.9)	8 (33.3)	<0.0001

Frequency of HLA B51 n (%)	83/170 (48.8)	1/8 (12.5)	0.046
NS = non significant			

Table 4: Comparison in BD patients with and without cerebral vein thrombosis (CVT).

All patients with DVT were immediately treated with heparin or low weight molecular heparin during an average period of ten days. Acenocoumarol was introduced as soon as possible (in 2 or 3 days) and continued for at least 6 months. Corticosteroids were added in 105 patients with DVT and were systematically associated to immunosuppressive agents in all cases of VCT, HVT and CVT according to a strategy: 6 monthly intravenous pulses of cyclophosphamide followed by azathioprine 2 mg/kg.

DVT recurrence was significantly less frequent in patients for whom corticosteroids were added to anticoagulants (22% vs. 59.3%; p<0.0001). One death related to venous thrombosis was noted in our patients. It was a patient with Budd Chiari syndrome who died probably from hepatic failure. Two other deaths were noted in patients with DVT; one was related to an aneurysm rupture and the second to renal amyloidosis.

In our study, prothrombotic disorders weren't systematically screened because BD diagnosis, as a major cause of the DVT, was often evident. C protein, S protein and antithrombin were tested in 12 patients, they were normal in all cases. Antiphospholipid antibodies were negative in 12 patients and positive with low rates in 4 patients. Plasma homocysteine level was measured in 40 patients with DVT and was high is 19 patients with a mean rate of 22.89 µmol/l +/- 5.01. There were no differences in hyperhomocysteinemia in patients with and without DVT (36.8% vs. 47.5%; p =0.34).

Comments

Although vascular lesions are not included in ISG criteria for BD, our results and other reported investigations indicate that up to 40% of patients are likely to develop this complication. Among them DVT were the most frequent [5]. This high frequency probably encouraged experts to develop new criteria including vascular lesions such us the International Criteria for Behçet's disease (ICBD) [11] to improve criteria sensitivity.

In our series, 27.6% of BD patients (79.3% of patients with vascular involvements) had DVT.

This frequency varies from 6 to 40% depending on the ethnicity and countries of studied population. In BD, DVT is evidently more frequent in Mediterranean countries: 21.9% in Italy [5], 29.8% in Turkey [12] and 24.9% in another Tunisian series [9]. The highest frequency was reported in Egypte: 41.2% in a series of 63 patients [13]. DVT is less frequent in Asia (Korea and Japan), North and South American (United States of America and Brazil) where only 6 to 15% of BD patients had DVT [4,14-16].

Our study confirms the male predominance reported in all previous studies [17,18]. The delay between the occurrence of DVT and the first symptom of BD was 4.32 years. The critical period for developing DVT was 2 to 3.2 years after the diagnosis of BD [19,20]. Koç and al noticed that the frequency of vascular lesions appears to have a tendency to decrease after 5 years from the time of BD diagnosis [20].

Lower extremities are the most frequent location of DVT (noted in 68% in our series) as reported in all previous studies [6,17]. It can be isolated or associated to other thrombosis especially inferior vena cava thrombosis [20,21].

Behçet's disease is a main cause of VCT. In our study, VCT were observed in 29 patients and as in other studies, it constituted the second location of DVT. In the literature, VCT frequency in BD varies from 7.6 to 33% [6,7,13]. Superior and inferior cava are equally involved (respectively 18 and 16 patients). Male predominance was more evident in patients with VCT.

It seems that venous thrombosis in BD run a slow and insidious course over time, since vena cava thrombosis was usually diagnosed after development of venous collaterals. The frequent association, at diagnosis, of superior and inferior vena cava thrombosis with respectively jugular veins (66.6%) and lower extremities (81%) or hepatic veins (37.5%) is another argument that these thromboses developed insidiously and extend slowly [22].

HVT, which is classic but very rare in BD was reported in 0.3 to 2.8 % of cases. But BD is one of the most frequent causes of Budd-Chiari syndrome, accounting for roughly half of such patients [19]. HVT may cause Budd-Chiari syndrome and carries a high mortality rate due to liver failure [19,23]. Among our 6 patients with this complication, one died because of liver failure. Thus, in BD patients with inferior VCT, HVT should be systematically investigated and treated precociously to avoid complications.

Cerebral venous thrombosis (CVT) is a major manifestation of BD. However, its frequency is difficult to ascertain from the literature, which consists mainly on single case reports or short series [24,25]. In our series, 5.5% of our BD patients presented this complication. This frequency was similar to the one reported by Saadoun and al in a group a BD patients selected in a French department [24]. In this study, 7.8 % of BD patients had CVT; among them 50 % were North African. The diagnosis of CVT was considered in symptomatic patients with either headache, intracranial hypertension, and/or other neurologic manifestations. Comparison between patients with and without CVT, showed a higher frequency of arterial involvements and of parenchymal central nervous system lesions but a lower frequency of ocular involvement in those with CVT. whereas, in the French study and others [24-26], the CVT were not associated with neurological parenchymal lesion. Male predominance was not found in this group of patients.

Prothrombotic disorders weren't screened in all our patients but were absent in all cases when tested. Antiphospholipid antibodies were negative or considered as negative because they were at low rates. As shown in most large studies, there was no significant difference in terms of coagulation parameters between patients with and without thrombosis [27,28]. Besides, we think that the insidious course of DVT in BD is supporting the hypothesis that endothelial injury is the main abnormity in BD thrombosis, and not the thrombophilic factors positivity. Although some studies suggested that hyperhomocysteinemia may be associated to thrombosis in BD patients [29], in ours series, hyperhomocysteinemia was not correlated to DVT.

There were no prospective placebo-controlled trials in the treatment of DVT in BD and treatment is usually based in experts' recommendations. Two drugs were recommended in the management of DVT: corticosteroids and immunosuppressive therapy [1]. In our patients, corticosteroids decrease the risk of DVT recurrence and

Desbois et al. showed that use of glucocorticoids and other immunosuppressive agents prevent venous thrombosis relapse in BD patients [30].

For most authors, there is no evidence of benefit in anticoagulation. Ahn et al. found no differences between patients treated with anticoagulant associated to immunosuppressant and those who had only immunosuppressive therapy [31]. Some authors use anticoagulant in the acute phase of VT to prevent extension of the thrombosis. Controlled trials are needed the codified DVT treatment.

In conclusion, DVT were frequent in our group as in most Mediterranean countries, male predominance was evident in our patient with DVT and the outcome was good in these patients after treatment.

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