Deep vein thrombosis in Behcet's disease

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ABSTRACT Objective

We aimed to describe the epidemiologi cal and clinical aspects of deep vein thrombosis (DVT) in Behçet's disease (BD) and to determine the patients at high risk for this complication. Methods

Among 113 patients with BD according to the international criteria for classifi cation of BD, those with DVT were ret rospectively studied. The diagnosis of DVT was made in all cases using con ventional venous angiography, venous ultrasonography and/or thoracic or ab dominal computed tomography. Pa tients were divided in two subgroups according to the occurrence of DVT other than cerebral thromboses. The medical records of these patients were reviewed in order to investigate their past medical history and evaluate their response to the treatment prescribed. Clinical and genetic factors (HLA B51 and MICA 6) that might contribute to DVT were analysed by comparing pa tients with and without DVT. Results of our series were compared to those of other series in the literature. Statistical analysis was by Chi square with neces sary correction and Fischer tests.

Results

Forty-four patients (38.9%) had deep vein thrombosis of various systems with 81 localisations. There were 40 men and four women (mean age 28.1 years; range 17-60). DVT appeared after the onset of disease with a mean delay of 3.8 years. In 6 cases, DVT revealed BD. When we evaluated the risk of DVT coexistence with other clinical findings and genetic factors (HLA B51 and MICA 6), we found a significant positive correlation with sex, and positive pathergy test.

Conclusion

In our series, occurrence of DVT was significantly associated with male gen der and positive pathergy test.

Introduction

Behçet's disease (BD) is a multisystem disorder characterised mainly by recurrent oral and genital ulcers and ocular involvement. Neurologic and vascular involvement are not rare and may be life-threatening. Vein thromboses constitute the most frequent vascular manifestation seen in 6.2 to 33 % cases of BD (1, 2). We carried out this study to determine the frequency, the clinical characteristics and course of deep vein thrombosis (DVT) in BD patients and to define a subgroup of patients at high risk for this complication.

Patients and methods

The medical records of one hundred and thirteen patients with BD were reviewed in order to investigate the patient's medical history, the clinical manifestations and outcome of the disease as well as the treatment prescribed. The diagnosis of BD was made based on the criteria established by the international study group for BD (3). Patients were divided in two subgroups according to the occurrence of DVT other than cerebral thrombosis. The diagnosis of DVT was made using venous ultrasonography in all cases, with abdominal computed tomography in 8 cases for inferior vena cava thrombosis (IVCT) and thoracic computed tomography in 4 cases for superior vena cava thrombosis (SVCT); conventional venous angiography was performed in one case. Protein S, protein C and anti-thrombin III levels were determined in all patients. The anticardiolipin (aCL) and antiß2 Glycoprotein1 antibodies (B2GP1) were measured in 24 patients by ELISA using IgG isotype. HLA-B51 allele was determined in 38 patients using a complement-dependent microlymphocyte toxicity assay; fifteen of these patients had DVT. Triplet repeat polymorphism of MICA was analysed on a denaturating polyacrynamide gel and alleles were visualised by autoradiography in 34 patients, 11 of whom had DVT. Results in both subgroups were compared by Chi-square with necessary correction and Fischer tests.

Results

Of 113 patients with BD, 49 (43.3%) had vascular involvement. Among them 44 (38.9%) patients had DVT, 7 arterial aneurysms and 6 arterial thromboses. Seven patients presented both venous and arterial involvements. The group of patients with DVT consisted

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of 40 men and four women whereas the group of the remaining 64 patients without DVT was composed of 37 men and 27 women. Male predominance was significantly higher in the DVT patient group (p = 0.0004). Mean age of patients at the moment of diagnosis of BD was roughly similar for patients with (28.1 years) and without DVT (32 years). The average delay to diagnosis of DVT from the date of BD diagnosis was 3.1 years (range 0-18 years). DVT revealed BD in 6 cases. Eighty-one locations of DVT were detected. Fortythree patients showed more than one location. Twelve patients had a vena cava thrombosis (VCT) among them only one had both superior and inferior VCT. Hepatic venous thrombosis (Budd-Chiari syndrome) was seen in 5 patients. Clinical features of BD in patients with and without DVT are summarised and compared in Table I. Pathergy test was significantly more frequently positive in patients with DVT (p = 0.030). Protein C, protein S and anti-thrombin III levels were normal in all patients. Seven of 24 patients were positive for IgG aCL with no difference between patients with and without DVT, and no patient was posi-DVT and thirteen patients without DVT were HLA B51 positive, the difference was not statistically significant (p = 0.480). Eight patients with DVT and twenty patients without DVT were MICA 6 positive, the difference was not statistically significant either (p =0.287).

All patients were treated with anticoagulant agents and colchicine (1mg/day). The anticoagulant consisted of a standard intravenous heparin during ten days followed by acenocoumarol. Corticosteroids were prescribed to 20 patients and monthly intravenous pulses of cyclophosphamide were indicated in 5 cases (two with IVCT and 3 with SVCT). Complete clinical recovery from DVT was noticed in 24 cases (77%), signs of chronic venous insufficiency (increased leg circumference, dermatitis, hyperpigmentation and skin ulceration) were seen in 6 patients. Recurrence of thrombosis was observed in 9 cases and one patient died of severe

Table I. Clinical and genetic features of BD patients with and without DVT.

	Behçet's disease with DVT n = 44	Behçet's disease without DVT n = 64	Р
Male	40 (90.9%)	37 (57.8%)	0.0004
Age (years)	28.4	32	0.562
Buccal aphtosis	43 (97.7%)	64 (100%)	0.407
Genital aphtosis	33 (75%)	48 (75%)	0.821
Pseudofolliculitis	25 (56.8%)	30 (46%)	0.412
Pathergy Test	34 (77.2%)	37 (57%)	0.036
Erythema nodosum	20 (45.4%)	34 (53%)	0.556
Ocular involvement	14 (31.8%)	30 (46%)	0.112
Articular involvement	26 (59%)	44 (68%)	0.407
Neurological	8 (18.1%)	6 (9%)	0.231
HLA B51	11 (25%)	13 (20%)	0.480
MICA 6	8 (18%)	20 (31%)	0.287

Budd-Chiari syndrome. Of 20 patients with DVT treated with corticosteroids, 5 showed recurrence of thrombosis, while 4 of the remaining 24 patients had this complication (p = 0.72).

Discussion

Although vascular lesions are not included in the major diagnostic criteria of BD, our results and other reported investigations indicate that 1/4 to 1/2 of patients are likely to develop this complication (2, 4). Venous thrombosis appeared to be the major vascular involvement reported in 7 to 33% of cases with BD, and representing 85 to 93% of vasculo-Behçet. It is significantly more frequently observed in Arab and European populations (19-34%) (5) than in Asian non-Arab populations (7-12.5%) (6).

Our study confirms the male predominance reported by all previous studies and which varied from 2.6% to 4.4% (7). The mean age of patients with vascular involvement varied from 25 (7) to 30 years (4) with no significant difference between the sexes as found in our study. The reported most critical period for developing DVT was 2 to 3.2 years after the diagnosis of BD (4,7) and that is in agreement with our results (3.1 years). And, as noticed by Koç et al. (4) the frequency of vascular lesions appears to have a tendency to decrease after 5 years from the time of BD diagnosis

Our study indicates that DVT affects most frequently the lower extremities

(62% of cases) and this result is also in agreement with those reported by Wechsler (8). The second most common localization of DVT was the vena cava, observed in 10 patients. VCT was reported in 0.2 to 10%, more frequently in West Mediterranean and European patients (9). In our study, 6 patients had hepatic venous thrombosis which is a very rare complication of BD reported in 0.3 to 2.8 % of cases (7).

In this study, pathergy positivity was the only statistically significant clinical feature which is more frequently observed in BD patients with DVT compared with those without DVT. A higher prevalence of positive pathergy test and erythema nodosum in vasculopathy BD had also been previously reported by Koç (4) and Muftüoglu (2) from Turkey.

It is well known that HLA B51 is the most important genetic factor associated with BD in many ethnic groups (10). But studies of the association of HLA B51 with specific manifestations of BD showed controversial results (10-12). In this study, the association of HLA B51 with DVT was not found. MICA 6 allele has recently been shown to be significantly associated with BD in Japan (13). But studies of the association of MICA polymorphism with specific manifestations of BD were very rare and failed to show such an association (11). In our study too, no association of BD with MICA 6 was found.

The mechanism of vein thrombosis in BD remains unknown. Several studies

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failed to associate specific coagulation abnormalities with this disease (14). In our study, neither deficiency in protein C, protein S and anti-thrombin III nor resistance to activated protein C, aCL and aB2GP1 levels seemed to be correlated with vascular thrombosis in BD. Hence, thrombosis in BD seems to be related more to vasculitis than to clotting disorders. The optimal treatment of vascular thrombosis in BD remains controversial. antiplatelet agents such as low-dose aspirin and dipyridamole are recommended in cases of venous involvement, but a controversy exists on this subject. Koç did not recommend Aspirin to patients with BD in view of their results, which showed reduced biosynthesis of prostacyclin in BD (4). As we think that vascular changes leading to vasculitis and thrombosis are important pathological features of BD (15), we recommend and administer corticosteroids in all cases of DVT, associated with immunosuppressive therapy in cases with vena cava or cerebral venous involvement.

According to our results and to previously reported investigations (2,4,7), we can conclude that DVT occurs more frequently in males patients with positive pathergy test and erythema nodosum.

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