Prevalence of Behçet's syndrome in patients presenting with venous thrombosis: prospective study in a cardiovascular outpatient clinic

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Abstract

Introduction: Behçet's syndrome (BS) is a vasculitis characterized with oral and genital ulcers and uveitis. Vascular involvement is a serious cause for mortality and morbidity including both arteries and veins of all sizes. The aim of this study was to determine, the prevalence of BS among patients presenting with deep vein thrombosis (DVT) in routine cardiovascular surgery outpatient clinic.

Material and methods: One hundred and sixteen patients presenting with signs and symptoms of DVT in our cardiovascular surgery outpatient unit were reviewed between 2005 and 2007. All the patients were searched for the symptoms of BS: history or presence of oral aphthae, genital ulcers, uveitis, erythema nodosa, arthritis or arthralgia, and thrombophlebitis. Routine laboratory blood tests as well as specific thrombotic markers were checked. Pathergy skin test was performed and evaluated at 48 h in suspected individuals.

Results: Nine patients were diagnosed with BS. The prevalence of BS among patients presenting with a clinic of DVT in our cardiovascular outpatient unit was 7.5%. Only one of the patients with BS was female. The mean age of the patients was 38.9 years (range: 29-62 years). The patients with BS were significantly younger than the non-BS patients ($p < 0.05$). Interestingly, only one patient with DVT was previously diagnosed as BS.

Conclusions: It is important to keep in mind the differentital diagnosis of Behçet's syndrome in a cardiovascular outpatient clinic.

Key words: thrombosis, deep vein thrombosis, vasculitis, Behçet's disease.

Introduction

Behçet's syndrome (BS) is a vasculitis characterized with oral and genital ulcers and uveitis. After its first description by Hulusi Behçet in 1937, additional target organ involvements, including neurologic, gastrointestinal, pulmonary, arterial, and venous have been recognized and added to the disease spectrum [1, 2]. Vascular involvement is a serious cause for mortality and morbidity characterized by involvement of both arteries and veins of all sizes. Lower extremities are the most common sites for deep or superficial venous involvement [3-5]. Review of these different clinical manifestations by factor analysis has shown the superficial and deep vein thromboses to be a separate factor among all the other clinical manifestations of BS [1]. Thus, it is important to keep in mind the

differential diagnosis of BS in a cardiovascular surgery outpatient setting, especially in a country where the prevalence is high.

Our aim in this study was to determine the prevalence of BS among patients presenting with deep vein thrombosis (DVT) in routine cardiovascular surgery outpatient clinic.

Material and methods

One hundred and sixteen patients presenting with clinical signs and symptoms of DVT were evaluated prospectively between 2005 and 2007 in cardiovascular surgery outpatient unit of Gazi University, Ankara, Turkey. The patients were examined at the outpatient clinic by a cardiovascular surgeon. All the patients were questioned for the symptoms of BS: history or presence of oral aphthae, genital ulcers, uveitis, erythema nodosa, arthritis or arthralgia, and thrombophlebitis. Pathergy skin test was performed and evaluated at 48 h in suspected individuals. The diagnosis of BS was made according to the criteria of the International Study Group for Behçet's disease (Table I) [6].

All the patients were applied routine laboratory tests including complete blood count, clotting parameters [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], blood biochemistry [fasting blood glucose, hepatic functions, renal functions, electrolytes (Na^+, K^+, Ca^{2+})], lipids, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) as well as specific tests in suspected cases such as HLA-B5, anti-cardiolipin antibodies, and protein C and protein S. Doppler ultrasonography (USG) was performed on the both extremities. Additional diagnostic radiological work-up (angiography) was performed in cases suspected of a cerebrovascular event. Abdominal USG was performed to rule out the presence of an intra abdominal mass or thrombosis of the inferior vena cava. If pulmonary embolism was suspected, ventilation perfusion scintigraphy was performed. Treatment was initiated with intravenous heparin infusion. Following heparin infusion (adjusted dose, target PTT 1.5-2.5 × control PTT), anti-aggregant therapy was initiated. All the patients with BS were started on azathioprine 2.5 mg/kg/day for immunosuppresion. All other causes of DVT were treated with appropriate dose of warfarin (adjusted dose, target INR 2.5-3).

Table I. International Study Group Criteria for the diagnosis of Behçet's disease

Recurrent oral ulceration
Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least 3 times in one 12-month period
Plus two of the following criteria:
Recurrent genital ulcerations
Aphthous ulceration or scarring observed by physician or patient
Eye lesions
Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination *or* Retinal vasculitis observed by ophthalmologist
Skin lesions Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions *or* Acneiform nodules observed by physician in post-adolescent patients not on corticosteroid treatment
Positive result on pathergy skin test Read by physician at 24-48 h

** Findings applicable only in the abscence of other clinical explanations*

Statistical analysis

Statistical analyses were performed using Sigma Stat software version 3.0 (SPSS Inc., Chicago, USA). The results are expressed as mean ± standard deviation of the mean. Overall comparisons between the groups were performed by using one-way analyses of variance (ANOVA) method that applies post-hoc multiple Holm-Sidak tests, and by using the non-parametric Kruskal-Wallis (failing normality) or post-hoc multiple Dunn tests. *P* values < 0.05 were considered statistically significant.

Results

Among 116 patients, nine patients were diagnosed with BS. The clinical features of the patients diagnosed with BS are summarized on Tables II, III. The prevalence of BS among patients presenting with deep vein thrombosis to our cardiovascular outpatient unit was 7.5%. Of all the DVT cases, 64 (55.1%) were male, and 52 (44.82%) were female. Among the nine BS cases, eight (88.8%) were male, and only one was female. The mean age of all the patients was 50.5 years (range: 19-86 years). The mean age of the patients diagnosed as BS and non-BS was 39.8 years (range: 29-62 years) and 47.5 years (range: 19-86 years), respectively. The patients with DVT and BS were significantly younger than the non-BS patients ($p < 0.05$). All patients with BS presented with a clinic of DVT. Excluding a 62-year-old patient who already had the diagnosis of BS 12 years previously, all patients were primarily diagnosed.

The values of the BS and non-BS patients for the parameters of complete blood count, clotting, blood biochemistry and lipids were not statistically significantly different. The patients with BS had significantly elevated ESR and CRP levels when

Table II. The clinical features of BS in 9 patients with BS and venous involvement

Sings	Number of cases
Oral aphthae	9
Genital ulcers	6
Uveitis	1
Erythema nodosum	0
Osteofolliculitis	2
Arthritis and arthralgia	4
Superficial thrombophlebitis	2
Gastrointestinal involvement	0
Central nervous system	1
Positive pathergy skin test	4

compared to the non-BS patients [ESR: 37.3 ±4.7 vs. 18.9 ±7.5 mm/h, p = 0.023; CRP: (normal: 0-6 mg/l) 47.09 ±5.1 vs. 14.8 ±4.2 mg/l, p = 0.012]. In four of the BS patients, HLA-B5 series were positive.

In 21 non-BS DVT patients (18%), an etiology could be identified. These were anti-phospholipid syndrome in nine patients (7.5%) and a tumor in the remaining (10%). The ESR and CRP levels of the BS patients and the patients with neoplastic disorders or anti-phospholipid syndrome were not statistically significantly different ($p > 0.05$ for both).

Doppler USG revealed thrombosis at the lower extremity in 115 of 116 patients. The most frequent sites of thrombosis in the veins of the lower extremity veins (Figure 1) were: the popliteal vein (n = 36, 31.03%), the femoro-popliteal vein (n = 32, 27.58%), the femoral vein (n = 30, 25.86%), the iliac and common iliac veins (n = 15, 12.93%), and the inferior vena cava (n = 2, 1.72%). The vascular involvements of patients with BS are summarized in Table III. Patients with BS differed in their vascular involvement from other causes of DVT in their diffuse type of involvement of the vessel wall. Pulmonary artery aneurysm was observed in one BS and DVT patient.

Discussion

The prevalence of BS in general population differs in 'Silk Road' region where Turkey has the highest prevalence: 8-42 per 10 000 [7]. In this study, the prevalence of BS in patients presenting with a clinic of DVT in a tertiary cardiovascular outpatient setting was determined as 7.5%. The patients with BS and DVT were much younger than the patients with other causes of DVT were. Moreover, almost all of the patients with BS and DVT were male (the mean age of the patients with vascular involvement was 38.9, years and the

Table III. The vascular involvement sites of the patients with BS

Patient no.	Gender	Age	Site(s) of vascular involvement
1	Male	62	Femoral
2	Male	36	Femoral, iliac, inferior vena cava
3	Male	48	Femoral, iliac
4	Male	29	Iliac vein, inferior vena cava
5	Male	43	Saphaneous, popliteal, femoral
6	Male	29	Internal jugular, brachiocephalic, superior vena cava
7	Female	42	Popliteal
8	Male	30	Saphenous, femoral, popliteal, brachial, cephalic
9	Male	38	Popliteal, femoral, sagital and transverse sinus

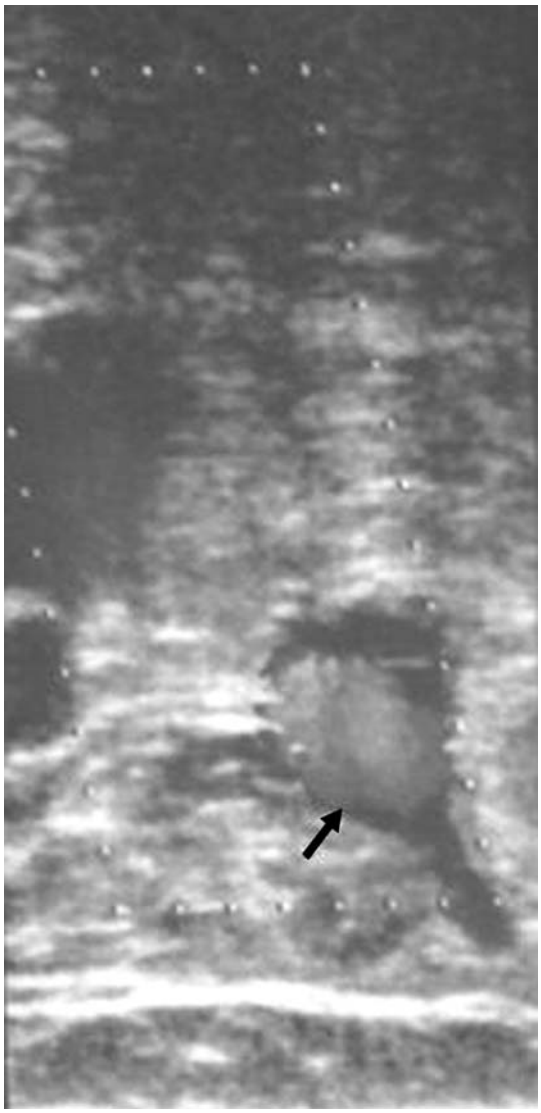

Figure 1. Thrombosis in the femoral vein by Doppler USG

male/female ratio was 8/1). These findings are consistent with earlier literature showing that vascular involvement in BS mostly occurs in males at their third or fourth decade [8].

Most frequent clinical features of BS are oral and genital apthae followed by skin lesions like erythema nodosum and acne-like lesions. Eye, vascular and neurological involvements are the most serious and young males are at more risk for developing these features. One third of the patients with BS have major involvement beyond vasculitis [9, 10]. Although the vasculitis of BS can affect both venous and arterial systems, venous system is involved more frequently. Deep vein thrombophlebitis is the most frequent vascular manifestation of BS, and the most commonly involved site is the lower extremities followed by the superior vena cava, the inferior vena cava, and the upper extremities [11]. Thrombosis of the iliac veins and of the superior and inferior (or both) vena cavae can sometimes be seen together, with the formation of collateral vessels [12]. A recent study surveyed large vessel involvement in BS retrospectively in 883 patients [13]. Most of the vascular events occurred within the first 5 years of disease onset. In 35% of these patients a second vascular event occurred. Strikingly, in 30% of the patients, the vascular event was either present or preceded the disease onset. Overall, a second vascular event occurred in 313 patients (35%), and after the first event, 5 year probability of a second event was around 30% [13]. In one of our patients, DVT developped at disease onset. In 4 of our patients, DVT recurred; in 3 of these, recurrence occurred within 5 years of the first attack.

The pathogenesis of thrombosis in BS is still not clear. Deficient protein C and protein S, antiphospholipid antibodies, antithrombin, mutations for factor V Leiden, prothrombin gene G20210A, methylenetetrahydorfolate reductase gene C677T were implicated as procoagulant mechanisms for thrombosis. However, studies concerning a pro-coagulant pathogenesis have been inconclusive. Another important factor in the pathogenesis of thrombosis is fibrinolytic activity. Tissue-type plasminogen activator (t-PA), which synthesizes plasmin from plasminogen, is an important step in initiating the fibrinolytic system. Studies for fibrinolysis have produced inconclusive results as well. The reason for these varying results may be due to patient selection and differing laboratory techniques [14]. Most studies concerning thrombosis in BS have not included positive controls such as patients with other inflammatory diseases or thrombosis due to other reasons. In a study by Yurdakul *et al*. [14], t-PA, plasminogen activator inhibitor (PAI-1) and d-dimer levels were evaluated in 10 BS patients with acute DVT, 25 BS patients with chronic DVT, 27 patients with ankylosing spondylitis, 15 patients with acute DVT due to other causes, 10 patients with sepsis, 26 patients with diffuse systemic sclerosis and 23 healthy controls. They have found lower levels of t-PA in BS patients with acute DVT compared to patients with DVT due to other causes. D-dimer levels were similar in BS patients with DVT and patients with DVT due to other causes. PAI-1 did not differ between the groups. Therefore, the authors suggested that the tendency of thrombosis in BS may be due to a defect in fibrinolytic activity [14].

Endothelial damage is another possible mechanism for thrombophilia in BS. Pathologically, the active vasculitis stage of BS is characterized by intense infiltration of acute inflammatory cells, particularly involving the media and adventitia [15, 16]. Postmortem examinations of the venous system have revealed thrombus that adheres to the vessel wall tightly. This may be the reason for almost the nil occurrences of pulmonary emboli in BS [17, 18].

The major angiographic findings of vascular involvement of Behçet's disease were acute or chronic deep vein thrombosis within the tributary veins of lower extremities, pseudoaneurysms of the large or medium-sized arteries, and occlusions/stenoses of the distal run-off arteries of the lower extremities. Common findings on computerized tomography are obliterated or thrombosed deep veins and noncalcified thickened aneurysmal walls with or without curvilinear enhancement. The combination of these findings and the clinical manifestations are helpful in distinguishing vascular Behçet's disease from other vasculitides [18, 19].

There is no agreement on the therapy of deep venous thrombosis of BS. Unlike other causes of DVT, there is no proven effect of anti-coagulation therapy for the thrombus of BS. Furthermore, anticoagulation therapy has major side effects. As thrombus is tightly adhered to the vessel wall, and the occurrence of pulmonary embolism is almost nil in BS, the aim of the treatment is to reduce inflammation of the vessel wall and prevent recurrences. Thus, immunosuppressive therapy is favored in BS by some investigators rather than anti-coagulation [17]. In an interesting long-term follow-up study by Hamuryudan *et al*. [19], patients who participated in a double-blind placebo-controlled study with azathioprine were re-evaluated after 94 (± SD 10) months. In addition to long-term beneficial effects for ocular symptoms, authors have observed that extra ocular symptoms, especially vascular events, occurred considerably more in the placebo group [20]. In a small retrospective study by Ahn *et al*. [21], 37 patients with DVT and BS were retrospectively analyzed in 3 treatment groups: i) immunosuppressive therapy only, ii) combination of immunosuppressive therapy, and anticoagulation, and iii) anticoagulation only.

There were more recurrences in the anti-coagulation group than in the other treatment groups. The authors have speculated that anticoagulation may not be necessary for the treatment of DVT in BS [21]. In our study group, all the patients diagnosed with BS received azathioprine 2.5 mg/kg/day with anti-aggregant therapy. All other causes of DVT were treated with appropriate dose of warfarin.

Differential diagnosis of DVT may reveal interesting results [22]. Distinguishing BS in a cardiovascular outpatient clinic is essential as the pathogenesis and the treatment of BS and DVT differ from those of other causes of DVT. We believe that especially in young male patients presenting with DVT, clinical signs of Behçet's disease should be sought for an accurate diagnosis and treatment.

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