Fibrinolytic activity and d-dimer levels in Behçet's syndrome

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ABSTRACT

Objective. *Thrombophlebitis occurs in a third of patients with Behçet's syndrome (BS). The thrombotic tendency in BS has been studied with inconclusive results perhaps due to the inadequate numbers of patients studied during the acute phase of the thrombosis as well as the lack of appropriate diseased controls. We have studied tissue-type plasminogen activator (t-PA) and its inhibitor (PAI-1), and d-dimer levels in BS patients with and without thrombosis both in the acute and chronic phases along with suitable diseased and healthy controls.*

Methods. *t-PA and PAI-1 were studied by ELISAand d-dimer by semiquantitative latex agglutination slide test in 30 BS patients without deep vein thrombosis (DVT), 10 BS with acute DVT (ADVT), 25 BS with chronic DVT, 27 with ankylosing spondylitis, 26 diffuse systemic sclerosis, 15 patients with ADVT due to other causes, 10 patients with sepsis, and 23 healthy controls.*

Results. *The t-PA levels in BS with ADVT were significantly lower than those in patients with ADVT due to other causes (7.4 ± 6.2 vs. 13.4 ± 6.3, P = 0.027) while PAI-1 levels did not show significant differences between the groups (P= 0.60). The numbers of patients with d-dimer levels of ≥ 0.5 μg/ml in BS with ADVT were similar to those found in patients with ADVT due to other causes (9/10 vs. 14/14).*

Conclusion. *The relatively low t-PA levels point to a defect in fibrinolysis in BS. d-dimer levels are increased in the acute phase of thrombosis in BS.*

Introduction

Venous involvement occurs in one third of patients with BS. Thrombophlebitis of deep and superficial veins of the legs are followed in frequency by thrombosis of both superior and / or inferior *vena cavae* (1- 4).

The pathogenesis of thrombosis in BS is not clear. Endothelial damage and/or defects in coagulation or fibrinolysis are thought to play a role (5).

Deficient Protein C and protein S, antithrombin, procoagulant mutations like factor V Leiden, prothrombin gene G20210A, methylenetetrahydrofolate reductase gene C677Tand the presence of antiphospholipid antibodies have all been implicated in the pathogenesis. The results of these studies however have been somewhat conflicting and inconclusive (6-13).

The synthesis of plasmin from plasminogen is an important step in the activation of the fibrinolytic system and requires tissue type plasminogen activator (t-PA) or urokinase type plasminogen activator (u-PA). Inadequate t-PA secretion from the endothelium and increases in the levels of its inhibitor plasminogen activator inhibitor (PAI-1) may result in an insufficient fibrinolytic system and may increase the risk of thrombosis.

d-dimer is the degradation product of cross linked fibrin that is formed by the action of plasmin and its levels increase in acute thrombosis, various prothrombotic and inflammatory states (14-20).

Studies of fibrinolysis in BS have also been contradictory. t-PA antigen levels have been found to be normal (21-23), decreased (24,25) or increased (26) and t-PA activity was reported as normal (12, 21), decreased (24) or increased (23). Normal (12,25) or increased levels of PAI-1 antigen (21-23) and normal (24) or increased (21, 23) levels of PAI-1 activity have also been reported. In addition, positive correlations between the clinical activity of BS and the levels of PAI-1 (21, 22) and a negative correlation between the clinical activity and t-PA levels have been shown (22). d-dimer levels did not differ between 18 patients with BS and 14 sero-

negative arthritis in one study (21) and similarly they did not show differences between BS (n = 33) and normal controls (n = 30) in another (25). In the last study d-dimer levels were lower in 5 patients with BS who had superficial thrombophlebitis compared to patients with BS who did not have thrombophlebitis (25).

The main drawbacks of these studies were that none included an adequate number of patients with BS during the acute phase of thrombosis. Also suitable positive controls such as patients with thrombophlebitis due to other causes and patients with other inflammatory diseases were lacking.

Our aim in the current work was to measure the t-PA, PAI-1 and d-dimer levels in patients with BS who had acute and chronic deep vein thrombosis and to compare them with appropriate controls: patients with other inflammatory conditions such as systemic sclerosis, ankylosing spondylitis, sepsis, acute deep vein thrombosis due to other causes and healthy controls. We also investigated the relation of these findings to clinical activity measures in BS and to acute phase parameters such as erythrocyte sedimentation rate (ESR) and high sensitive CRP(hsCRP).

Patients and methods

Between February 2001 and March 2002 we studied 143 patients and 23 healthy controls. The groups were:

1. BS without any history or any clinical findings of deep vein thrombosis (DVT) at the time of study (Behçet DVT negative, n=30),
2. BS with acute DVT (Behçet ADVT, n = 10) studied within 7.7 ± 4.9 days of the onset of their thrombotic attacks,
3. BS with chronic DVT(Behçet CDVT, n = 25) involving thrombosis of calf and/or superior or inferior vena cavae, all BS patients fulfilling the International Study Group Criteria for diagnosis (27),
4. Ankylosing spondylitis patients (n = 27) diagnosed according to the modified New York criteria (28),
5. Diffuse systemic sclerosis fulfilling the criteria for the diffuse form (n = 26) (29, 30),
6. Patients with ADVT (n = 15) due to causes other than BS including 2 patients with cancer, one with retroperitoneal fibrosis, and one with diabetes mellitus, all studied within 5.4 ± 4.8 days of their thrombotic attacks,
7. Sepsis patients (n = 10) fulfilling the definition of sepsis criteria (31), and
8. Healthy controls (n=23) (Table I).

ADVT was confirmed by Doppler ultrasonography in all patients. Chronic DVT in patients with BS was clinically apparent and/or confirmed by Doppler ultrasonography or computerized tomography.

When blood samples were taken, drug use among the patients and controls were as follows: nonsteroidal anti-inflammatory drugs in Behçet DVT negative (n = 3), Behçet ADVT (n = 1), ankylosing spondylitis (n= 24), and diffuse systemic sclerosis (n = 4); low dose aspirin (≤ 300 mg) in Behçet ADVT (n = 3), Behçet CDVT (n = 7), and diffuse systemic sclerosis (n = 4); heparin in Behçet ADVT(n= 1) and ADVTdue to other causes (n = 3); warfarin in Behçet CDVT (n = 1) and ADVT due to other causes (n = 2); both warfarin and heparin in ADVT due to other causes (n= 1); both warfarin and aspirin in Behçet ADVT (n = 1) and Behçet CDVT (n = 1).

The blood samples were drawn in the morning hours by venipuncture from the antecubital vein without venocclusion. ESR and hsCRP were measured in the first blood tubes.

For t-PA, PAI, and d-dimer determinations, 9 ml of blood was transferred through a 19 G needle to polypropylene tubes containing 1 ml 0.109 M trisodium citrate. Plasma was obtained by centrifugation at 4°C for 10 minutes at 3000 g and stored at -80°C until tested. For hsCRP measurement serum specimens were kept at -20°C until tested.

Plasma concentrations of t-PA and PAI-1 were determined by enzyme linked immunoabsorbent assay (ELISA) using the commercially available kits containing mouse monoclonal antibodies (Asserrachrom® tPA, Diagnostica Stago, France, Lot 003031 and Asserrachrom PAI-1, Diagnostica Stago, France, Lot 012651). Levels of d-dimer were determined by a semi quantitative latex agglutination slide test using mouse monoclonal antibodies for d-dimer in plasma (D-Di Test®, Diagnostica Stago, France, Lot 011301). No agglutination of undiluted plasma corresponded to a level of d-dimer of < 0.5 µg/ml, agglutination of undiluted plasma to ≥ 0.5 ≤ 1.0 µg/ml, agglutination of 1:2 diluted plasma to ≥ 1.0 ≤ 2.0 µg/ml, agglutination of 1:4 diluted plasma to ≥ 2.0 ≤ 4.0 µg/ml, agglutination of 1:8 diluted plasma to ≥ 4.0 ≤ 8.0 µg/ml, and agglutination of 1:16 diluted plasma to ≥ 8.0 g/ml. The cut-off value for d-dimer was ≥ 0.5 µg/ml.

hsCRP levels were determined by nephelometry (BNA2, Dade-Behring, Marburg, Germany).

All laboratory investigations were done blind to the identity of the subject and disease groups.

A clinical activity index was calculated for patients with BS by a modified index proposed by Yazıcı *et al*. (32). The presence of any oral and genital ulcers, erythema nodosum, and arthritis of each joint were counted as one point each. Vascular involvement was graded as follows: 1 = unilateral calf vein thrombosis (cvt) and/or superficial thrombophlebitis (st); 2 = bilateral cvt and/or st; 3= cvt and/or st requiring bed rest; 4 = thrombosis of vena cava superior (vcs) and/or vena cava inferior (vci); 5=thrombosis of vcs and vci, and/or arterial involvement as originally proposed. Additionally, the score of acute thrombophlebitis was added to the score of chronic thrombophlebitis in patients who had acute thrombophlebitis superimposed on CDVT. Differing from the original index, involvement of each eye was counted as 1 point irrespective of the degree of involvement and the number of follicular lesions were graded as 0 = no lesions, 1 = 1 - 5 lesions, 2 = 6-15, and 3 ≥ 15 lesions.

The study was approved by the Institutional Review Board of Cerrahpasa Medical Faculty and written informed consent was obtained from all individuals studied.

Statistics

The group comparisons were made by ANOVA. Paired values were evaluated

Table I. Demographic characteristics of patients, levels of acute phase reactants, PAI-1, and t-PAand the frequency of d-dimer of ≥0.5 μg/ml*.

	Behçet DVTnegative n = 30	Behçet acute DTV n = 10	Behçet chronic DVT n = 25	Ankylosing spondylitis n = 27	Diffuse systemic sclerosis n = 26	Acute DVTdue to other causes n = 15	Sepsis n = 10	Healthy controls n = 23
Age (yrs.)	29.1 ± 8.5 (18 – 55) (22 – 76)	34.0 ± 8.7 (19 – 53) (22 – 50)	32.5 ± 8.1 (23 – 56)	36.2 ± 8.5 (25 – 59)	47.8 ± 11.9 (28 – 66)	52.7 ± 14.2 (20 – 79)	51.0 ± 25.4	31.0 ± 7.2
Female/male	13 / 17	0 / 10	1 / 24	4 / 23	25 / 1	6 / 9	4 / 6	11 / 12
Disease duration (yrs)	3.7 ± 3.2 (0 – 10)	3.9 ± 4.8† (0 – 14)	6.2 ± 6.0 (1 – 22)	12.3 ± 7.5 (1 – 30)	8.8 ± 8.1 (0.5 – 35)	†		
ESR	37 ± 28 (5 – 115)	62 ± 27 (15 – 100)	44 ± 34 (5 – 110)	34 ± 15 (10 – 60)	41 ± 31 (5 – 120)	52 ± 43 (3 – 145)	57 ± 30 (24 – 125)	8 ± 6 (2 – 25)
hsCRP(mg/L)	2.3 ± 2.6 (0.04 – 13.3)	6.9 ± 2.9 (3.4 - 13.6)	3.7 ± 4.2 (0.07 – 17.3)	2.1 ± 1.4 (0.23 – 5.2)	1.1 ± 1.3 (0.06 – 4.9)	8.0 ± 8.4 (0.07 – 29.0)	16.0 ± 7.2 (5.9 - 31.9)	0.3 ± 0.7 (0.02 - 3.4)
PAI-1 ‡ (ng/ml)	27.1 ± 28.3 (2.1 – 156)	25.1 ± 17.3 (7.0 – 52)	43.5 ± 47.3§ (2.0 – 160)	38.7 ± 37.3 (0.8 – 144)	35.5 ± 28.6 (7.0 – 112)	42.0 ± 40.6 (6.8 – 145)	42.6 ± 34.4 (1.0 – 130)	31.4 ± 29.1 (2.8 – 110)
t-PA¶ (ng/ml)	7.1 ± 7.5§ (1 – 34)	7.4 ± 6.2# (2 – 18.4)	5.6 ± 4.3 (1 – 19)	9.0 ± 6.3 (1 – 23)	9.0 ± 7.0 (0.5 – 25)	13.4 ± 6.3 (3.3 – 23)	15.8 ± 16.3 (1 – 50)	5.8 ± 5.4 (1 – 27)
d- dimer$	14 / 30 (47)	9 / 10 (90)	18 / 25 (72)	7 / 27 (26)	16 / 25 (64)	14 / 14 (100)	7 / 9 (77)	5 / 22 (23)

* Values are mean ± SD (range) where indicated otherwise; yrs: years; †: The duration of thrombosis was 7.7 ± 4.9 days in BS with ADVTand 5.4 ± 4.8 days in patients with ADVTdue to other causes; ‡: P= 0.60 among all groups by ANOVA; ¶: P= 0.0009 among all groups by ANOVA; #: P= 0.027 vs those with ADVTdue to other causes by Student-t test; §: one patient missing; $: number of patients with ≥0.5 μg / ml /tested (%)

by the Kolmogorov-Smirnov test. Correlations were compared by parametric Pearson and non-parametric Spearman tests. Data were expressed as the mean and standard deviations (± SD).

Results

The sex, mean age, ESR, hsCRP, PAI-1, t-PA and the number of patients with d-dimer levels of ≥ 0.5 μg/ml are presented in Table I. There was a significant difference among the t-PA levels (P = 0.0009) while the PAI-1 levels did not show significant differences among the groups (P = 0.60). The levels of t-PA among patients with BS who had ADVT were significantly lower than the patients with ADVT due to other causes (7.4 ± 6.2 vs 13.4 ± 6.3, P = 0.027). There were no significant differences in the levels of t-PA and PAI-1 among the subgroups with BS (Table I).

d-dimer levels are shown in Table II. The frequency of positive results did not differ between patients with BS who had ADVT and patients with ADVT due to other causes when ≥ 0.5 μg/ml was taken as the cut-off value (9/10, 90 % vs. 14/14, 100%) (Table I). There was also no difference in the frequency of semiquantative d-dimer levels between the two groups (P = 0.351) (Table II). The frequency of d-dimer of ≥0.5 μg/ml was 72% (18/25) in patients with BS who had chronic DVT and 47% (14/30) in BS patients without thrombophlebitis.

BS clinical activity was 7.0 ± 4.1 in the group without thrombophlebitis, 7.2 ± 1.6 in the ADVT, and 7.0 ± 3.7 in the group with chronic DVT.

There were no significant correlations between t-PA, PAI-1, d-dimer and clinical activity as well as the acute phase reactants (ESR and hsCRP) among the three BS groups studied (data not presented).

There were also significant correlations between d-dimer and hsCRP (P = 0.025) in ADVT due to other causes

Table II. Semiquantitative d-dimer levels.

d-dimer*	Behçet DVT negative n = 30	Behçet acute DVT n = 10	Behçet chronic DVT n = 25	Ankylosing spondylitis n = 27	Diffuse systemic sclerosis n = 25	Acute DVTdue to other causes n = 14	Sepsis n = 9	Healthy controls n = 22
0	16	1	7	20	9		2	17
1			2		1	1		
2	6	5	8	5	8	2	3	2
4	2				1	2		
8	1	1	5	2		3	1	2
16	5	3	3		6	6	3	1

* : 0 = < 0.5 g/ml; 1 = 0.5 - < 1.0 g/ml; 2 = 1.0 - < 2.0 g/ml; 4 = 2.0 - < 4.0 g/ml; 8 = 4.0 - < 8.0 g/ml, and 16 = ≥ 8.0 g/ml.

Table III. Previous studies on fibrinolytic activity on Behçet's syndrome.

Author, year (references)	Study groups	PAI-1 activity (IU/ml)	PAI-1 antigen (ng/ml)	tPAactivity (IU/ml)	tPAantigen (ng/ml)	d-dimer (ng/ml)	Additional comments
Aitchison, 1989 (24)†‡	Behçet, n = 7 Oral aphthae, n = 12 Healthy, n = 10	23 → 3 15.5 → 8.5 9.5 → 5.2		7.8¶ →12.2 mm§ 9.3 → 13.0 10.2 → 13.6	3.2¶ → 6.4¶ 5.2 → 9.9 7.3 → 10.4		Varying responses among BS without Tbp (n = 3) and with TB (n = 4) (duration
Hampton, 1991 (21)†	Behçet, n = 18 Seronegative arthritis, n = 14	9.1¶¶ 5.1	13.9¶¶ 6.4	100 100	8.8 7.45	< 200 < 200	No differences between BS without Tbp (n = 11) and with Tbp (n = 7) (duration?)
Ozoran, 1995 (22)	Behçet, n = 63 Oral aphthae, n = 30 Healthy, n = 30		52.8 ±19.9¶¶¶ 52.8 ± 14.3 36.1 ± 15.8		5.6 ± 2.4 6.2 ± 1.9 6.2 ± 2.3		
Orem, 1995 (25)	Behçet, n = 33 Healthy, n =30		63.8 ± 27.9 58.1 ± 21.2		4.2 ± 1.2¶ 5.8 ± 2.1	463 ± 97 486 ± 106	↓ d-dimer in 5 with Tbp (duration?) vs without Tbp (n = 28)¶ in BS.
Haznedaroglu, 1996 (23)†#	Behçet, n = 30 Healthy, n = 15	11.2¶ →12.4→11.7 6.7→ 8.1→7.3	62¶ →54→51 41→40→ 41	3.4¶ →2.8→1.1 0.9→0.7→0.4	12.1→10.2→ 4.2 12.6→10.2→ 4.6		None had Tbp
Demirer, 2000 (26)	Behçet, n = 127 Healthy, n = 24				7.72 ± 3.58¶ 5.25 ± 1.84		
Espinosa, 2002 (12)	Behçet, n = 38 Trombosis, n = 38 Healthy, n =100		21 ± 12 16 ± 11 20 ± 12	2 ± 1 3 ± 1 2 ± 1			No differences between BS without Tbp (n = 24) and with Tbp (n =13) (duration?)

* Values are mean ± SD where indicated otherwise; † : median; ‡ ; values of baseline and after venous occlusion test for 10 minutes, respectively (arrows); ¶ : P < 0.05 vs healthy controls; ¶¶ : P < 0.002 vs diseased controls; ¶¶¶ : P < 0.001 vs healthy controls; § : euglobulin fibrin plate lysis; Tbp: Thrombophlebitis; ↓ : decreased; # : values of baseline, 30 and 120 minutes after DDAVPstimulation, respectively (arrows).

and between d-dimer and ESR (P = 0.018) in systemic sclerosis.

Discussion

In this study t-PA levels were significantly lower in patients with BS who had ADVT compared to patients with ADVT due to other causes (Table I). The levels of d-dimer were equally high among BS patients with ADVT and patients with ADVT due to other causes (Tables I and II). There was no relationship between the levels of t-PA, PAI-1, and d-dimer and clinical activity among all three BS groups.

We believe that the lack of a significant increase in the levels of t-PA in BS patients with ADVT compared to those observed in patients with ADVT due to other causes is due to endothelial inflammation resulting in impaired fibrinolytic activity. In this respect our results are concordant with the studies that show an insufficient response of the endothelium to desmopressin acetate (DDAVP) (33). The variable levels of PAI-I and t-PA levels as reported in other studies (Table III) might have been due to patient selection and varying laboratory techniques (21-26). As already mentioned, BS patients with ADVT and positive controls selected among patients with thrombosis due to other reasons and with other inflammatory diseases were not included in previous studies (12, 21-26). In most of these studies the duration of thrombosis of BS was also not specified (12, 21, 22, 24-26).

Two other groups have also studied the d-dimer levels of patients with BS. Hampton *et al*. (21) have reported that there were no significant differences in the levels of d-dimer between 18 patients with BS (5 patients with a history of thrombosis, 2 with thrombosis during the follow-up and 11 patients without thrombosis) and 14 patients with seronegative arthritis. However, the duration of thrombosis and whether it was superficial or deep was not specified. In another study, Örem *et al.* (25) have shown that there were no significant differences between 33 patients with BS and 30 healthy controls. They have also shown that the levels of d-dimer were lower in 5 BS patients with superficial thrombophlebitis of unspecified duration compared to patients without thrombosis (Table III). Our results however showed that the frequency of positivity as well as the quantity of d-dimer were similarly high among BS patients with ADVT as the patients with ADVT due to other causes (Tables I and II).

Elevated d-dimer level is a sensitive tool for diagnosing pulmonary emboli. However, it should be cautiously interpreted in BS since elevated levels were found in BS patients with both acute (90%) and chronic thrombophlebitis (72%) as well as in patients without thrombophlebitis (47%) as seen in Tables I and II. A high d-dimer level may easily mislead the clinician to the diagnosis of pulmonary emboli. This in turn leads to inappropriate and potentially hazardous anticoagulation in a BS patient with thrombophlebitis especially when the patient complains of

heamoptysis. In this situation pulmonary aneurysm(s) due to pulmonary vasculitis must be the primary consideration. Pulmonary emboli are not common in the clinical spectrum of BS and the management of pulmonary aneurysms in BS requires administration of systemic immunosuppressives (34, 35). Our study was cross-sectional and to support causality it will be necessary to confirm our findings longitudinally. The semi-quantitative method of d-dimer measurement and the high positivity among the normal controls are other issues that need addressing. It is widely appreciated that d-dimer levels have a low specificity for any disease condition and different commercial kits can produce differing results (36). Our measurements, however, have been performed by an experienced technician in a blinded manner and similar problems with methodology were present in all groups studied.

A further point to consider is the fact that our t-PA measurements represented antigen levels rather than activity and we believe further similarly controlled studies are needed to look at the relation between t-PA antigen levels and activity as they relate to BS in its differing clinical forms. Two studies in the past looked at these parameters in parallel (21, 23). Neither study reported a formal correlation between the two while neither of these studies included patients with acute thrombosis. We appreciate that studying patients with acute thrombosis of BS can prove to be rather difficult and the number of such patients we could investigate even in a dedicated center in one year was limited only to a dozen. Nevertheless this is the largest series reported thus far.

In our study the overall clinical activity was similar among the groups with BS. We did not find any relationship between the fibrinolytic parameters and the clinical activity and the acute phase reactants such as ESR and CRP among BS groups as a whole. Previous studies, however, had shown a positive correlation between clinical activity and PAI-1 levels (21,23) and a negative correlation between clinical activity and t-PA levels (23). These differences may also be attributed to differing patient selection patterns and laboratory techniques.

The variations among sex, mean age, ESR and hsCRP among the groups were in accordance with different patient characteristics peculiar for different diseases. Our main goal was to include the relevant control groups seen in a rheumatology practice.

In summary, in this cross sectional study, t-PA levels were lower in BS with ADVT compared to patients with ADVT due to other causes. This was probably due to endothelial damage in BS and the resulting insufficient t-PA response. d-dimer levels were similarly high in patients with BS who had ADVT as the patients with ADVT due to other causes. The increased level of d-dimer with the relatively low t-PA levels suggests a defect in fibrinolysis in the acute phase of thrombosis in BS.

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