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REVIEW

Behçet's disease and thrombophilia

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Behçet's disease (BD), first described in 1973, is characterised by recurrent oral and genital ulcers as well as eye inflammation. Other features of this chronic multisystem inflammatory disease include neurological, cardiovascular, pulmonary, gastrointestinal, musculoskeletal, and dermatological involvement.¹

Venous or arterial thrombosis occurs in 25% (10–37%) of patients.² Venous thrombosis is more common than arterial thrombosis (88% *v* 12%).³ Deep and superficial venous thrombosis of the legs predominates.^{4–7}

Arteritis is treated with a combination of corticosteroids and cytotoxic agents. Anticoagulants and antiplatelet agents are used for deep venous thrombosis, though there has never been a properly controlled study to justify this treatment in BD.⁸

The thrombin-antithrombin complex (TAT) is a marker of intravascular thrombin formation. Prothrombin fragments 1+2 (PF1.2) are peptide fragments generated when prothrombin is activated to thrombin. TAT and PF1.2 are both biological markers of thrombin generation and thus correlate with thrombotic risk.^{9–10}

Several studies have shown increased levels of PF1.2 and TAT in patients with BD.^{11–12} These alterations probably reflect the activation of the coagulation cascade in these patients and are not the cause of the thrombosis.

Vasculitis, the main pathological process in BD, can partially explain the thrombotic phenomena.¹³ Why such thrombosis is not so common in other vasculitides, and why it occurs in only about 25% of patients with BD, is still unclear.

As knowledge about the cause of venous and arterial thrombosis is growing, it is now clear, that thrombosis may result from a combination of hereditary and acquired abnormalities. It is speculated that a combination of abnormalities of procoagulants, anticoagulants, and fibrinolytic factors, together with the vasculitis and

the endothelial injury, accounts for the clinical thrombosis in this subgroup of patients with BD.

The present review is a critical summary of the published data about these matters in patients with BD. A literature search was conducted on an electronic database (Medline) and the bibliography of existing articles was hand searched. Table 1 shows the available data.

Endothelial injury

Vascular endothelium has procoagulant, anticoagulant, and fibrinolytic properties. Vascular endothelial cells play the most critical part in the defence against thrombosis.¹¹

The pathological hallmark of BD is a non-specific vasculitis of veins, arteries, and capillaries in all affected organs. Vasculitic lesions are characterised by perivascular lymphocyte and mononuclear cell infiltration, endothelial oedema, degeneration of the elastic lamina interna, fibrinoid necrosis, and deposition of immune complexes within the vascular wall.¹⁴ The inflammation usually affects all layers of the vessel wall with very adherent thrombi in the lumen. For this reason, although large segments of the vessel wall are affected, pulmonary emboli are quite rare in BD. Pulmonary disease consists mainly of pulmonary artery thrombi, infarcts, aneurysms, and arteriobronchial fistula.¹⁵ Endothelial cell injury due to vasculitis seems to be a key event in the prethrombotic state of BD.^{16–17}

Significantly higher plasma levels of von Willebrand factor (vWF) and tissue plasminogen activator (tPA)—both endothelial products—have been reported in several studies of patients with BD compared with controls.^{18–24} Demirer *et al* found significantly higher levels of tPA and vWF in 127 patients with BD compared with 24 healthy age matched controls.²⁴ Moreover, levels of tPA and vWF were found to be higher in the subgroup of patients with vasculitis and

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Table 1 Suggested abnormalities in clotting, coagulation, and fibrinolysis in patients with Behçet's disease (BD) with thrombotic complications—comparison with other patients with BD and with controls. (Only significant data are represented)

Analysed factor	Prevalence among control patients	Prevalence among all patients with BD	Prevalence among patients with thrombosis	Prevalence among patients without thrombosis	Reference	Comments
Anticoagulant factors						
Leiden factor (% (No))	10 (11/107)	23 (15/64)	37.5 (12/32)	9 (3/32)	Gul <i>et al</i> (4)	Results revalidated in few clinical trials
APCR‡ (% (No))	5 (16/320)	29 (17/58)	67 (6/9)	22 (11/49)	Kosar <i>et al</i> (19) Espinosa <i>et al</i> (32)	Another study confirmed these results. Increased plasma concentration in patients. May point to decreased concentration on endothelial cells and decreased function
Thrombomodulin (mean values) (ng/ml)	26.7	35				
Procoagulant factors						
Homocysteine (% (No))	9 (4/43)	28 (12/43)	31 (10/32)	3 (1/32)	Altınbas <i>et al</i> (50) Gul <i>et al</i> (56) Mader <i>et al</i> (29)	No significant difference between patients groups Comparison between patients. No controls Most studies confirmed these results, but specific antibody assays were not significant ⁴⁵
Prothrombin mutation (PT20210) (% (No))	5 (1/20 patients with RA)	40 (10/25)				
Anticardiolipin antibody (% (No))						
Fibrinolytic pathway						
Lp(a)‡ (mean value) (g/l)	0.18	0.3	0.52	0.21	Orem <i>et al</i> (25)	Same study shows other fibrinolytic anomalies: increased PAI-1 and decreased tPA in patients with Behçet's disease
tPA‡ (mean (SD) value) (ng/ml)	30 Pt‡ 5.8 30 Pt	33 Pt 4.2* 33 Pt	5 Pt 4.78* 5 Pt	28 4.6 28 Pt	(25)	
PAI-1† (mean value) (ng/ml)	5.25 (1.84)	7.72 (3.52)	8.16 (2.89)	7.57 (3.81)	Demirer <i>et al</i> (24)	
Endothelial injury	24 Pt 58.1† 24 Pt	127 Pt 63.8† 33 Pt	34 83 5 Pt	93 Pt 59.4 28 Pt	(25)	
Mean (SD) vWF‡ (50%–160% scale) (%)	88.2 (30.7)	108.9 (40.2)	121.8 (54.8)	104.3 (32.4)	(24)	Same patient group showed increased vWF and tPA and decreased thrombomodulin indicators of endothelial damage

*Differences between patients with BD with and without thrombosis were not significant.

†Differences between patients with BD and controls were not significant.

‡APCR = activated protein C resistance; Lp(a) = lipoprotein (a); tPA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor; vWF = von Willebrand factor; Pt = patients.

thrombosis compared with other patients with BD. It may be speculated that a leakage from damaged endothelial cells causes the increased levels of vWF and tPA.^{18–23}

Fibrinolytic pathway

Plasmin, the key enzyme of the fibrinolytic system, is effectively inhibited by α_2 -antiplasmin, forming a plasmin- α_2 -antiplasmin complex (PAP), a molecular marker of fibrinolytic activity.^{12, 16} Significantly higher plasma levels of PAP were found in patients with BD.¹² Haznedaroglu *et al* found even higher plasma levels of PAP in the group of patients with BD with vascular manifestations.¹² Orem *et al* reported lower levels of tPA in 33 patients with BD compared with 30 controls, without any significant difference between the subgroups of patients with BD.²⁵ These patients had raised levels of the fibrinolytic inhibitors, lipoprotein (a) (Lp(a)) and plasminogen activator inhibitor (PAI-1), with significantly higher levels in patients with BD with a history of thrombosis compared with those with BD without thrombosis. Lp(a) has been found to cause a twofold enhancement of PAI-1 secretion from cultured human endothelial cells, while having no effect on tPA production.²⁶ Studies of patients with BD have suggested that reduced tPA and increased PAI-1 secretion from endothelial cells (as a result of vascular damage) may be responsible for diminished fibrinolysis in these patients.^{21, 27}

Anticoagulant factors

The association between natural inhibitors of coagulation, and thrombophilia is well known but the role of low protein S, protein C, or antithrombin III levels in the pathogenesis of thromboembolic complications in BD is debated. Most studies were unable to demonstrate lower levels or reduced activity of these proteins.^{24, 27–30} In a study of 30 patients with BD, protein S was found to be even higher than in the control group. However, antibodies to protein S were found in 50% of these patients, suggesting that this may be an autoimmune, acquired condition. Interestingly, more than half of these patients had thrombosis.

THROMBOMODULIN

Thrombomodulin is an endothelial factor involved in the activation of protein C, and thereby in inhibition of the coagulation cascade. It has been suggested that a low concentration of thrombomodulin, especially in combination with factor V Leiden mutation, increases the risk for thrombotic complications.³¹ Demirer *et al* reported lower levels of thrombomodulin in 127 patients with BD compared with healthy controls. No difference was found between patients with BD with thrombotic complications and patients with BD without such complications.²⁴ However, Espinosa *et al* described higher levels of thrombomodulin in patients with BD as compared with controls, and found no correlation with any thrombotic tendency.³²

LEIDEN FACTOR AND ACTIVATED PROTEIN C RESISTANCE

The most common inherited coagulation defect associated with venous thrombosis is activated protein C resistance (APCR).³³⁻³⁴ Most cases of APCR are caused by a point mutation at nucleotide 1691 in the factor V gene (arginine 506 to glutamine), referred to as the Leiden factor. Gul *et al* found the factor V gene mutation in 15/64 (23%) patients with BD, compared with 11/107 (10%) healthy controls group.⁴ Furthermore, the mutation was found in 12 (37%) of the "thrombotic" patients with BD compared with three (9%) in the "non-thrombotic" BD group. Other authors confirmed these results later.³⁵⁻³⁶

Kosar *et al* measured APCR in 58 patients with BD and found APCR in 17 (29%) patients compared with 5% (16/320) in the healthy controls.¹⁹ Sixty seven per cent of the patients with BD with a history of thrombosis were APCR positive, as compared with 22% of the patients with BD without thrombosis (table 1).

Furthermore, factor V Leiden was found to be significantly higher in patients with BD and ocular disease.³⁷ The highest expression of factor V Leiden mutation was found in patients with retinal disease.

Procoagulant factors

ANTIPHOSPHOLIPID AND ANTICARDIOLIPIN ANTIBODIES

Antiphospholipid antibodies (aPL) are a heterogeneous group of antibodies that include antibodies directed against pure phospholipids, antibodies against coagulation related phospholipid binding proteins (β_2 -glycoprotein I, prothrombin, annexin V, protein S), and antibodies against complexes of phospholipids and phospholipid binding proteins.³⁸⁻³⁹ It is well known that aPL are associated with arterial and venous thrombosis.⁴⁰ The reported frequency of aPL in patients with BD is quite variable (0–46%).⁴¹⁻⁴⁶

Mader *et al* detected higher plasma levels of IgG anticardiolipin antibodies (aCL) in 10/25 (40%) patients compared with a control group (5%).²⁹ However, no correlation with thromboembolic complications was found. In a similar study, nearly half of the patients with BD were found to have increased levels of aCL.⁴¹ Similarly, when the study was extended to include a meta-analysis of the available published data, it could be shown that nearly 30% of the patients with BD had raised levels of aCL. However, no correlation was found with specific disease manifestations, except for erythema nodosum. Hull *et al* found a significant association of retinal vasculitis in BD with aCL,⁴² but most other reports failed to find a correlation between aCL and any vascular event occurring in BD.⁴³⁻⁴⁶ Priori *et al* studied 29 patients with BD, 14 of whom had thrombotic events, and 29 healthy matched controls; they found a low prevalence of aCL and anti-annexin V antibodies in patients with BD. No significant association with thrombotic events was found.⁴⁷

A recent study included 128 patients with BD, the largest number of patients reported,

143 healthy controls, and 20 patients with systemic lupus erythematosus (SLE). The frequency of IgG and IgM aCL was found to be 2.4% in BD, 50% in SLE, and 5.6% in healthy controls. There was no significant association between aCL titres in patients with BD and vascular or ocular disease, disease duration, pathergy positivity, a high erythrocyte sedimentation rate, or immunosuppressive treatment.⁴⁸

HOMOCYSTEINE

Heterozygous hyperhomocystinaemia affects up to 0.3–1% of the general population, and is associated with recurrent deep venous thrombosis.⁴⁹ Altinbas *et al* found that 12/43 (28%) patients with BD and only 4/43 (9%) healthy controls had hyperhomocystinaemia.⁵⁰ The prevalence of thrombosis was 2/12 (17%). Eight patients with raised levels of homocysteine had neither APCR nor thrombosis.

PROTHROMBIN MUTATION

A guanine to adenine base substitution at position 20210 of the 3'-untranslated region of the prothrombin gene raises prothrombin levels.⁵¹ This mutation is associated with a threefold increased risk of venous thrombosis,⁵² and has been reported as the second most common inherited hypercoagulable state.⁵³ The prevalence of heterozygous 20210 carriers varies from 1% to 5% in healthy white population.⁵³⁻⁵⁵ In a study group consisting of 64 patients with BD, 32 of whom had a history of thrombosis, Gul *et al* found heterozygous prothrombin mutation in 10 (31%) of the patients with BD with thrombosis compared with just one (3%) in the patients with BD group without thrombosis.⁵⁶ Four patients in the former group were carrying both factor V Leiden and the prothrombin mutation. A total of 18 patients (56%) with vascular manifestations were carrying factor V Leiden or the prothrombin gene mutation, or both, compared with four patients without thrombosis. On the other hand, Espinosa *et al* tested 33 patients with BD, 11 of whom (33%) had thrombotic events. The heterozygous prothrombin mutation was found in only one patient with deep venous thrombosis, and in one healthy control subject.³¹ A recently published study obtained similar results: it found no association between the prothrombin gene mutation (as well as factor V Leiden mutation and methylenetetrahydrofolate reductase) and patients with BD with thromboses.³⁷

Conclusion

BD is a multisystem, relapsing chronic disorder of unknown cause. Non-specific vasculitis of the veins, arteries, and capillaries is common to all affected organs. Vascular disease and thrombosis is one of the most important features, and accounts for most of the mortality. Endothelial cell injury due to the vasculitis of BD seems to be the key event in the prothrombotic state of this disease.²³ Endothelial dysfunction relates to activation of platelets

(for example, by vWF), inhibition of fibrinolysis (raised PAI-1), and inhibition of natural anticoagulants (reduced thrombomodulin).

A substantial subgroup of patients with this prothrombotic state develop thrombosis. These patients probably have other defects—inherited or acquired—in the coagulation pathway, anticoagulant factors, and fibrinolysis.

The prevalence of aCL was higher (30–50%) in patients with BD than controls, but there was no correlation with the clinical occurrence of thrombosis. Other aPL were not found to be increased in BD.

Leiden factor or APCR was detected in up to 29% of patients with BD, and in up to 37.5% of patients with BD with thrombosis.

The prevalence of the prothrombin mutation 21210 gene in patients with BD with thrombosis is also high. One study found 31% of patients with BD with thrombosis had this mutation as compared with only 3% of the patients with BD without thrombosis.⁵⁶ Furthermore, 56% of patients with BD with thrombosis were found to have either factor V Leiden or the prothrombin mutation. The detection of the two most common hereditary prothrombotic mutations in more than half of the patients with BD with thrombosis supports the notion that procoagulant mutations have a role in the pathogenesis of thrombosis in BD. Nevertheless, the mere association of these abnormalities with patients with BD does not explain the thrombotic tendency in a substantial group of such patients. Thus there is further need to compare the prevalence of known coagulation factor abnormalities in patients with BD, with and without thrombosis, in idiopathic thrombosis, and in healthy controls. Such studies should provide a better understanding of the thrombotic tendency in BD, and may even disclose a genetic linkage between inherited thrombophilia and BD.

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