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. Venous or arterial thrombosis occurs in 25% (10–37%) of patients.

Venous thrombosis is more common than arterial thrombosis (88% vs 12%). Deep and superficial venous thrombosis of the legs predominates. 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.

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.

Several studies have shown increased levels of PF1.2 and TAT in patients with BD. 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. 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.

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. 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. Endothelial cell injury due to vasculitis seems to be a key event in the prethrombotic state of BD.

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. Demirel et al found significantly higher levels of tPA and vWF in 127 patients with BD compared with 24 healthy age matched controls. Moreover, levels of tPA and vWF were found to be higher in the subgroup of patients with vasculitis and
### 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)

<table>
<thead>
<tr>
<th>Analysed factor</th>
<th>Prevalence among control patients</th>
<th>Prevalence among all patients with BD</th>
<th>Prevalence among patients with thrombosis</th>
<th>Prevalence among patients without thrombosis</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant factors</td>
<td></td>
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<tr>
<td>Leiden factor (% (No))</td>
<td>10 (11/107)</td>
<td>23 (15/64)</td>
<td>37.5 (12/32)</td>
<td>9 (3/32)</td>
<td>Gal et al (4)</td>
<td>Results revalidated in few clinical trials</td>
</tr>
<tr>
<td>APCR (%)</td>
<td>5 (10/320)</td>
<td>29 (17/58)</td>
<td>67 (6/9)</td>
<td>22 (11/49)</td>
<td>Kosar et al (19)</td>
<td>Another study confirmed these results.</td>
</tr>
<tr>
<td>Thrombomodulin (mean values) (ng/ml)</td>
<td>26.7</td>
<td></td>
<td></td>
<td></td>
<td>Espimosa et al (32)</td>
<td>Increased plasma concentration in patients. May point to decreased concentration on endothelial cells and decreased function</td>
</tr>
<tr>
<td>Procoagulant factors</td>
<td></td>
<td></td>
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<tr>
<td>Homocysteine (% (No))</td>
<td>9 (4/43)</td>
<td>28 (12/43)</td>
<td>31 (10/32)</td>
<td>3 (1/32)</td>
<td>Akhtyamov et al (50)</td>
<td>No significant difference between patients groups</td>
</tr>
<tr>
<td>Prothrombin mutation (PT20210) (% (No))</td>
<td>31 (10/32)</td>
<td>31 (10/32)</td>
<td>31 (10/32)</td>
<td>3 (1/32)</td>
<td>Gul et al (56)</td>
<td>Comparison between patients No controls</td>
</tr>
<tr>
<td>Anticardiolipin antibody (% (No))</td>
<td>5 (1/20 patients with RA)</td>
<td>40 (10/25)</td>
<td></td>
<td></td>
<td>Mader et al (29)</td>
<td>Most studies confirmed these results, but specific antibody assays were not significant</td>
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<td>Fibrinolytic pathway</td>
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<td>Lp(a‡) (mean value) (g/l)</td>
<td>0.18 (normal = 3.1 g/l)</td>
<td>0.3</td>
<td>0.52</td>
<td>0.21</td>
<td>Orem et al (25)</td>
<td>Same study shows other fibrinolytic anomalies: increased PAI-1 and decreased tPA in patients with Behçet's disease</td>
</tr>
<tr>
<td>dPA (mean (SD) value) (mg/l)</td>
<td>5.8</td>
<td>3.3</td>
<td>5.1</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tPA‡ (mean (SD) value) (ng/ml)</td>
<td>5.25 (1.84)</td>
<td>7.72 (3.52)</td>
<td>8.16 (2.89)</td>
<td>7.57 (3.81)</td>
<td>Demirer et al (24)</td>
<td></td>
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<tr>
<td>Endothelial injury</td>
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<tr>
<td>Mean (SD) vWF‡ (50%–160% scale) (%)</td>
<td>88.2 (30.7)</td>
<td>108.9 (40.2)</td>
<td>121.8 (54.8)</td>
<td>104.3 (32.4)</td>
<td>(24) Same patient group showed increased vWF and tPA and decreased thrombomodulin indicators of endothelial damage</td>
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</table>

* 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.
Behçet's disease and thrombosis

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 (β₂-glycoprotein I, prothrombin, annexin V, protein S), and antibodies against complexes of phospholipids and phospholipid binding proteins. It is well known that aPL are associated with arterial and venous thrombosis. The reported frequency of aPL in patients with BD is quite variable (0–46%).

Mader et al detected higher plasma levels of IgG anticardiolipin antibodies (aCL) in 10/25 (40%) patients compared with a control group (5%). 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. 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, but most other reports failed to find a correlation between aCL and any vascular event occurring in BD. 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.

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.
(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 defect/s—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 21210G in patients with BD with thrombosis is also high. One study found 31% of the patients with BD with thrombosis.56 Furstis is also high. One study found 31% of patients with BD with thrombosis.

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The prevalence of the prothrombin mutation 21210G in patients with BD with thrombosis is also high. One study found 31% of the patients with BD with 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.

517–22.


52 Poort RS, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in 3’-untranslated region of prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698–703.