

Behçet's Disease as a Model of Venous Thrombosis

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Abstract: Behçet's disease (BD) is a chronic inflammatory disease of unknown aetiology characterized by recurrent oral, genital aphthous ulcerations, uveitis, skin lesions and other multisystem affections associated with vasculitis. Different types of vessels, predominantly veins, can be affected in BD. The frequency of vascular lesions in BD, such as superficial and deep venous thromboses, arterial aneurysms and occlusions, ranges between 7-29%.

In this review, various factors of thrombogenesis in BD, particularly pro- and antithrombotic endothelial and non-endothelial factors, factors of coagulation, platelet activation and rheological changes are presented and discussed from positions of Virchow's triad of venous thrombosis.

Despite advances in understanding of thrombogenesis in BD, still many issues of diagnosis and targeted preventive and therapeutic measures remain unresolved. Further studies are needed to clarify the pathobiology of BD-related thrombosis and to provide the clinicians with recommendations over the utility, safety and effectiveness of the antithrombotic therapy in BD.

Keywords: Behçet's disease, Thrombosis, Venous thrombosis, Arterial thrombosis, Vascular diseases, Virchow's triad.

INTRODUCTION

Behçet's disease (BD) is a chronic systemic disorder of unknown etiology characterized by recurrent oral and/or genital aphthous ulcerations, uveitis and skin lesions. Clinical presentation of this disorder is multifaceted and includes articular, central nervous system, gastrointestinal, renal, urogenital, pulmonary and cardiovascular manifestations, all of which are associated with systemic vasculitis, a pivotal pathophysiological feature of BD [1-4]. Recently, BD was classified into a group of auto-inflammatory disorders, sharing some common innate immune and genetic mechanisms of dysregulation of inflammation [5, 6], which can cause endothelial damage, activation of coagulation and thrombosis, and underlie vascular morbidity and mortality [7, 8].

Linked to the predisposing genetic and, possibly, environmental factors, cardiovascular pathology in BD represents a unique spectrum of inflammatory, thrombotic and aneurysmatic disorders. Importantly, vessels of any size and type can be affected, with venous pathology being recognized as a hallmark of the disease [9, 10]. The frequency of vascular involvement in BD (superficial and deep venous thromboses, arterial aneurysms, occlusions) ranges between 7-29% [9]. In a large observational study, it was shown that

about one quarter of patients with BD present with vascular involvement, of whom, only 12% with arterial pathology [11]. Though venous thrombosis of the lower extremities is thought to be the most frequent type of vascular pathology in BD, with the advent of new diagnostic techniques, such as magnetic resonance imaging, thromboses of other venous sites have been identified and reported in a series of recent observations (e.g. in superior and inferior vena cava, coronary, portal, renal, pulmonary veins) [12-15]. Aneurysmatic, pseudoaneurysmatic and thrombotic affections of large- and medium-size arteries, right-sided intracardiac thrombotic masses have also been reported, indicating complexity, life-threatening nature of thrombocoagulopathy in BD and importance of complex primary and secondary prevention [16-18].

In clinical practice, especially in the debut of BD, diagnosis and treatment of thrombosis is a challenge, requiring careful consideration of multiple thrombophilic factors and limited therapeutic options [19]. Based on experts' opinion, tight immunosuppressive therapy is, nowadays, a prerequisite of anti-thrombotic measures in BD. Anti-platelet therapy with aspirin is used in the most cases without major adverse effects. Experts, however, expressed caution over the use of anticoagulants, which can cause major bleedings (e.g. massive pulmonary haemorrhage from affected vessels) [1].

BD with its well-known tendency towards thrombosis and vasculopathy can serve as a clinical model of inflammation-related thrombosis. In this regard, investigation of

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factors and mechanisms involved in thrombosis in BD may have far-reaching implications for the whole group of auto-inflammatory disorders and cardiovascular prevention in the general population [20].

The aim of this review is to present some factors involved in thrombocoagulation in BD.

THROMBOGENESIS IN BD

Thrombogenesis in BD can be best viewed through the concept of Virchow's triad of venous thrombosis. Based on this concept, thrombus formation requires a combination of at least 2 out of 3 pathological components (abnormal blood flow, abnormal vessel wall, abnormal blood constituents) [21]. From this standpoint, BD can be viewed as a clinical model of venous thromboembolism. Abnormal blood flow due to the disturbances in microcirculation, increased blood viscosity are often coexisting with endothelial dysfunction, arterial aneurysms, venous varices, and numerous proinflammatory and prothrombotic changes of blood constituents. Direct damage of the endothelium, from one side, and vasculitis of vasa vasorum (more correctly, perivasculitis), from the other, cause destruction of vascular elastic structures and lead to aneurysm formation, further disrupt blood flow. Relapses of phlebitis with venous thrombosis eventually lead to post-thrombophlebitic syndrome with sustaining venous blood flow abnormalities.

Endothelial Factors

It is well known that in physiological conditions pro- and anti-coagulant endothelial activities are well balanced. Endothelial cell injury activates coagulation cascade by exposing subendothelial collagen, by releasing pro-coagulant endothelial agents, such as tissue factor (TF), von Willebrand factor (vWF), E-selectin, P-selectin and other adhesion molecules, thromboxane A₂ (TxA₂), the type-1 inhibitor of plasminogen activators (PAI-1), platelet activator factor (PAF), and by reducing activity of anti-thrombotics, such as prostacyclin (PGI₂), nitric oxide (NO), thrombomodulin, tissue plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), tissue factor pathway inhibitor (TFPI).

In a series of case-control studies, elevated levels of circulating vWF, a large multimeric glycoprotein, that binds and protects Factor VIII from degradation, and facilitates platelet adhesion, were found in patients with BD. Levels of vWF were especially high in those with thrombosis, who were also found to have highest levels of t-PA, a serine-protease responsible for clot destruction. All these shifts were triggered by endothelial damage [22-27].

Reduced levels of thrombomodulin, an endothelial membrane protein and co-factor of anticoagulant protein C, were shown to be associated to an increased risk of thrombosis in BD [28, 29].

Tissue factor pathway inhibitor (TFPI) is another endothelial protein, which reversibly inhibit Factor Xa (Xa) and thrombin (Factor IIa). Depletion of endothelial TFPI in BD was found in one study [30], while another study reported its elevation [31]. This discrepancy is, probably, due to laboratory measurements undertaken at different stages of disease activity.

An enhanced expression of E-selectin, adhesion molecule produced by endotheliocytes, was found in patients with BD with endothelial alterations at different sites (e.g. inflamed conjunctiva, erythema nodosum), and was associated with disease activity [32-37]. Immunosuppressive therapy was shown to reduce E-selectin levels in BD [37, 38]. It was also found that overexpression of E-selectin in BD is strongly and positively correlated with acute-phase reactants, such as C-reactive protein (CRP) [39].

Diminished production of nitric oxide (NO) by endothelial cells, known to reflect endothelial microvascular function, was found in patients with BD in some [40-43], but not all studies [44-46]. Production of NO and its release into circulation can be impaired because of ongoing inflammation and oxidative stress, a crucial pathophysiological component of active BD [47, 48]. Reduced bioavailability of NO may predispose to enhanced platelet aggregation eventually leading to thrombotic complications [47]. Genetic factors, namely single nucleotide polymorphisms of endothelial NO synthase (eNOS), can underlie endothelial dysfunction in BD. In fact, Glu298Asp polymorphism in exon 7 of eNOS associated to endothelial dysfunction, may explain the susceptibility of certain ethnic background to BD [49-52].

Another product of endothelial cells, endothelin-1, is a potent vasoconstrictor which antagonizes the effects of NO. Its involvement in vascular inflammation deteriorates vascular functions and leads to thrombosis. In patients with BD, high levels of this protein were found in association with disease activity and retinal vein occlusion [53-56].

Vascular endothelial growth factor (VEGF) is a marker of angiogenesis and endothelial dysfunction, which is produced by endothelial and some other cells in response to ischemia [57, 58]. In several small case-control studies, over-expression of VEGF was found in patients with BD [59-64], mainly during the active stage of the disease, in the case of ocular involvement and acute thrombosis. Attempts were made to associate VEGF gene polymorphisms with the development of BD and retinal vasculitis in Italian [65] and Korean [66] cohorts of patients, with conflicting results, probably, due to the ethnic differences.

TFPI is a Kunitz-type proteinase inhibitor, which is produced by endotheliocytes and released into the circulation upon stimulation by heparin. Its main function is to antagonize the effects of factor VIIa, factor Xa and thrombin. In one study, an increase of TFPI was found in BD patients, reflecting defensive activation of the system of antithrombosis [67]. In another study, its baseline levels in BD patients were normal, but the degree of stimulated by heparin release was lower compared with SLE patients and healthy controls [30].

Procoagulant Factors

Leiden point mutation in the gene of Factor V (Arg506Glu), causing resistance of Factor V to proteolysis by activated protein C, and the prothrombin gene G20210A mutation, leading to elevation of prothrombin levels, are common genetic factors associated with venous thrombosis in the general population [68]. Given the crucial role of these mutations in venous thrombogenesis, it was initially thought that these factors are culprits of prothrombotic state in BD.

However, in a multiple series of studies on the prevalence of these mutations among BD patients and possible association with disease activity, ocular involvement, thrombosis, homocysteinemia, CRP and other mutations related to coagulation, the obtained results were controversial [69-78]. For example, the prevalence of Factor V Leiden mutation was shown to vary among patients with venous thrombosis between 0 and 37.5% [69]. No association was found between Factor V Leiden, the prothrombin gene mutation, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, from one side, and CRP, homocysteine, factor VIII, from another [70]. In a recent meta-analysis of studies on Factor V Leiden, the prothrombin gene, MTHFR mutations and venous thrombosis in BD, the prothrombin gene mutation was found to be strongly associated with thrombosis (also after excluding results of Turkish studies) [79].

High levels of factor VIII, which is intimately involved in the coagulation cascade, were shown to be strongly associated with the risk of thrombosis in population-based studies [80, 81]. Importantly, factor VIII was independently associated with recurrent venous thromboembolism in non-BD subjects [82]. In cohorts of BD patients, the results were not equivocal [26, 70, 82-84], with the majority of studies, indicating elevation of plasma levels of this factor, alone or in association with vWF, which stabilizes factor VIII and, thus, enhances thrombogenesis [85].

Factor IX, another factor of coagulation, was found to be elevated in one case of a BD patient presented with intracardiac thrombus and pulmonary aneurysm [86].

Lipoprotein (a) is a low density lipoprotein, containing apolipoprotein B and apolipoprotein (a). Lipoprotein (a) exerts both atherogenic and anti-fibrinolytic effects [87-89]. Similar to plasminogen, lipoprotein (a) binds to fibrin [90, 91]. Elevated levels of lipoprotein (a) in BD were found in the most [92-95] but not all case-control studies [96]. Based on the obtained data [92-95], it is possible that this lipoprotein plays active role in vascular involvement and thrombosis in BD by stimulating the release of plasminogen activator inhibitor-1 (PAI-1) from endotheliocytes, resulting in hypofibrinolysis.

Antiphospholipid antibodies promote coagulation by acting against membranes phospholipids, by binding beta-2-glycoprotein I, prothrombin, annexin V, activated protein C, protein S and cross-reacting with thrombomodulin [97-100]. Pro-coagulant activity of these antibodies was associated with arterial and venous thromboembolism [97].

Many antiphospholipid antibodies were tested in BD [101-107], and except for a few small initial studies [101, 102], where elevated levels of anticardiolipin antibodies were associated with retinal and cerebrovascular pathology in BD, the majority of the studies failed to report elevation of antiphospholipid antibodies and association with thrombosis, suggesting that, unlike systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome, in this autoinflammatory disorder the role of autoantibodies is insignificant.

Anticoagulant Factors

Congenital deficiencies of anticoagulants, such as protein C, S (inhibitor of activated factor V and factor VIII) and antithrombin (inactivator of factor II and other coagulation

factors), predispose to thrombophilia in the general population. In BD, however, their involvement in thrombotic complications is insignificant [108-110].

Protein Z is another anticoagulant, a vitamin K-dependent protein acting as a co-factor in the pathway of activated factor X (FXa) inhibition. In one small case-control study, it was found to be decreased in patients with BD without vascular involvement [111].

Fibrinolytic Factors

Decreased fibrinolysis has long been recognized as a key factor implicated in coagulopathy in BD [26, 112]. Many case-control studies on t-PA in BD yielded conflicting results, indicating its decreased [93], increased [28] or unchanged activity [24, 73]. The majority of studies on PAI-1, however, found increased levels of this inhibitor of plasminogen activation in patients with BD with or without established thrombosis [93, 113]. Another inhibitor of fibrinolysis, thrombin activatable fibrinolysis inhibitor (TAFI), which is associated with venous thromboembolism in the general population, was assayed in patients with BD and found to be increased in one study [113]. PAI-1 and TAFI associated genetic polymorphisms were also tested in this study however there was not any association with BD.

Markers of Platelet Activation

Few studies investigated platelet function in BD [114-118] and found enhanced *in vitro* platelet aggregation in response to adenosine diphosphate (ADP) [114-116], impaired sensitivity of platelets to prostacyclin [23], overexpression of platelet bound P-selectin [117]. Patients with thrombosis demonstrated sustained overexpression of P-selectin and higher levels of platelet microparticles, and circulating microaggregates [118], which is suggestive of a role of platelets in thrombogenesis in BD. Importantly, in one small study, it also was found that the prevalence of 807TT genotype and 807T allele of the platelet glycoprotein Ia C807T/G873A gene polymorphism is higher in patients with BD compared with healthy controls, which may suggest genetically predetermined platelet hyperfunction in BD [119]. It should be, however, noted that these data were not uniformly confirmed, pending further more robust investigations.

Others Factors

It was suggested that disturbances in the blood rheology may also play a role in thrombosis due to BD. High plasma and blood viscosity, and enhanced erythrocyte aggregation, which are measures of impaired blood rheology, were noted in patients with BD [120, 121]. However, "blood flow abnormalities" in BD still need to be tested in patients with and without thrombosis, case-control and longitudinal studies.

CONCLUSIONS

Despite advances in understanding of diverse mechanisms of thrombogenesis in BD, there are still many unresolved issues of diagnosis and targeted preventive and therapeutic measures.

To date, the majority of studies on thrombosis in BD examined this issue fragmentally, concentrating on separate features without appreciating coexistence of diverse compo-

Table 1. Factors Involved in Thrombogenesis in BD and Possible Therapeutic Measures

	Factors of Thrombogenesis in BD	Therapeutic Measures
Blood flow abnormalities	Enhanced erythrocyte aggregation, increased fibrinogen, high blood viscosity Impaired microcirculation Turbulent blood flow at sites of venous varices and arterial aneurysms Arterial and venous occlusion	Immunosuppressive drugs Aspirin Heparin (?) Warfarin (?)
Abnormal vessel wall	Perivasculitis Endothelial dysfunction Venous varices Aneurysms and pseudoaneurysms	Immunosuppressive drugs Angioplasty (?)
Abnormal blood constituents	Endothelial factors (increase/decrease of vWF, t-PA, thrombomodulin, NO, VEGF, endothelin-1) Procoagulant factors [factor V Leiden and prothrombin mutations, hyperhomocystenemia, factors VIII, IX, lipoprotein (a)] Factors of fibrinolysis increase/decrease of TAFI, PAI-1, t-PA Anticoagulant factors (protein C, S, Z, TFPI, antithrombin) Platelets hyperactivity	Immunosuppressive drugs Heparin (?) Warfarin (?) Aspirin

nents of thrombosis. Accumulated evidence derived predominantly from multiple case-control studies suggests that all components of Virchow's triad of thrombosis, namely abnormal blood flow, abnormal vessel wall and abnormal blood constituents, are present in BD (Table 1). The time has come to investigate all these components together in large prospective cohorts of patients. It would be also useful to launch a multinational study, investigating implications of diverse environmental, genetic and acquired risk factors of thrombosis in different ethnic inceptive cohorts of patients.

The prevailing expert's opinion on the treatment of thrombosis in BD still supports immunosuppressive agents and is cautious over the use of anticoagulants, such as warfarin and heparin [122]. Uncertainties surround the issue of thrombolysis, anticoagulation and coronary angioplasty in acute coronary syndromes in BD [123]. Further studies, aimed to compare different antithrombotics and/or immunosuppressive agents on large samples, are warranted to provide the clinician with recommendations over the safety and effectiveness of antithrombotic therapy in BD.

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