Vascular Involvement in Behçet's Disease

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Behçet's disease is a systemic vasculitis of unknown etiology, characterized by recurrent oral and genital ulcers and uveitis [1]. In addition, cutaneous, articular, neurologic, intestinal, pulmonary, urogenital and vascular manifestations have been observed in these patients [2]. Given the heterogeneity of organ system involvement, five different sets of diagnostic criteria were in use until 1990. In that year, the International Study Group for Behçet's Disease published new criteria based on combined data from 914 patients at 12 institutions in 7 countries [3]. These criteria require the presence of recurrent oral ulceration plus any two of the following: recurrent genital ulceration, eye lesions, skin lesions, or positive finding on a pathergy test. Notably, the International Study Group also studied subcutaneous thrombophlebitis, deep vein thrombosis, and arterial aneurysm, but did not include them in the final criteria set because they lacked sensitivity, despite extremely high specificity for Behçet's disease. However, vascular system involvement, also called "vasculo-Behçet's disease," affects arteries, veins, and blood vessels of all sizes [4]; it has an estimated prevalence of about 25%, and includes venous and/or arterial thrombosis and arterial aneurysms [5].

Clinical manifestations

Large vessel involvement is observed in 15–35% of patients with Behçet's disease. In fact, the specificities of subcutaneous thrombophlebitis (95%), DVT (96%) and arterial aneurysm (98%) are higher for Behçet's disease than the specificities of eye lesions (93%) and most skin lesions (75%) [3]. Vasculo-Behçet may occasionally be the presenting manifestation of BD, making the diagnosis dificult [5,6]

Three major manifestations of vasculo-Behçet's disease have been identified: venous occlusion, arterial occlusion, and aneurysm formation, with a clear preponderance of the venous lesions (88%) compared to arterial involvement (12%) [5]. The coexistence of arterial and venous involvement is not infrequent and is one of the major causes of morbidity and mortality [7]. Vascular disease and some other clinical manifestations of BD disease appear to be gender-related. A survey of 137 Turkish patients with BD revealed 3% arterial and 24% venous involvement, the latter being more common in males [5]. A subsequent study of 2,400 Turkish patients confirmed the previous data – namely, that the risk of developing vascular complications is five-fold higher in male than female patients with Behçet's disease [8]. However, contradictory results on gender-related vascular involvement were obtained in series of Caucasian patients with BD [9].

Venous involvement

Venous involvement may range from superficial thrombophlebitis to DVT damaging large veins. The most frequent type of venous involvement in two reviews of the literature was subcutaneous thrombophlebitis [5,10], constituting 90% of all forms of vascular involvement in one of them [10]. DVT involving large veins is less frequent. Thrombosis of vena cava (superior and inferior) [11], occlusion of the suprahepatic veins causing Budd-Chiari syndrome [12] which carries a high mortality, and cerebral vein thrombosis [13] causing intracranial hypertension have been described. The sites of cerebral vein thrombosis, in decreasing order of prevalence, are superior sagittal sinus, one or both transverse sinuses, deep cerebral veins, and cavernous sinuses. Thrombi of Behçet's disease are usually adherent to the vessel walls, thus explaining the rarity of pulmonary thromboembolism in BD [14].

Arterial involvement

The prevalence of arterial occlusion in BD may range from 0.5 to 1.5% [5,15]. Starting with the aorta, the entire arterial tree can be affected. Peripheral arterial thrombosis may cause ischemic symptoms, intermittent claudication, and sometimes frank gangrene. Occlusion of the coronary, subclavian and carotid arteries can lead to myocardial infarction, pulseless disease, and stroke, respectively [16]. Renal artery involvement may cause hypertension, and pulmonary vascular occlusions may lead to pulmonary infarction and respiratory failure. Intracardiac thrombi [17], ventricular aneurysms, and silent myocardial infarction can be seen [18].

Aneurysms and arterial thrombosis may coexist [19]. The most common sites for aneurysm formation are the aorta and the pulmonary, femoral, popliteal, subclavian and common carotid arteries, but any artery can be affected [5,6]. Aneurysm rupture is the leading cause of death. Thrombophlebitis and multiple pulmonary arterial aneurysms, also known as Hughes-Stovin syndrome, should be considered a unique vascular manifestation of BD that causes a potentially lethal massive hemoptysis [4].

DVT = deep vein thrombosis
BD = Behçet's disease

Pathogenesis

The pathogenesis of thrombotic events in BD has not yet been clearly elucidated. Microscopic examination has identified vasculitis in both veins and arteries, but the etiology remains obscure. Antineutrophil cytoplasmic antibodies are generally negative in BD [20]. An interaction of an exogenous agent with the mononuclear cells from a genetically predisposed patient may result in damage and/or functional impairment of the vascular wall and a tendency to thrombosis. These include impairment of prostacyclin production, significantly higher levels of plasma endothelin-1,2, von Willebrand factor, and anti-endothelial cell antibodies in patients with vascular involvement [21].

The role of thrombophilic parameters such as protein C, protein S and antithrombin deficiencies, antiphospholipid antibodies and factor V Leiden have been analyzed in Behçet's disease with conflicting results [22,23]. Similar to thrombophilic parameters, the study of fibrinolysis has reported different and often conflicting results. Most of the hemostasis abnormalities found have been attributed to the endothelial injury secondary to vasculitis seen in Behçet's disease.

Protein C, protein S and antithrombin

The role of low levels of protein C, protein S or antithrombin in Behçet's disease is controversial. While values of protein C, protein S and antithrombin activity are generally normal in BD [22,24], two cases of BD with venous thrombosis and protein C or protein S deficiency have been described [25,26]. Two studies have reported a deficiency in antithrombin activity unrelated to thrombosis [22,27].

Methylenetetrahydrofolate reductase C677T mutation

The prevalence of methylenetetrahydrofolate reductase C677T mutation in Behçet's disease has been previously studied in only two series [28,29], with contradictory results.

Factor V Leiden

The prevalence of factor V Leiden in BD varies widely between the different series, ranging from 0% to 37.5% [22,23,30,31]. In one study, no significant differences were found in factor V Leiden prevalence compared to controls [22], whereas in another [30] it was significantly more frequent in BD but unrelated to venous thrombosis.

In contrast, an increased factor V Leiden prevalence in BD patients with venous thrombosis was found in two groups with a different ethnicity [23,31].

Prothrombin G20210A mutation

The prothrombin G20210A mutation has only been studied in two large series of BD. In one [28], no increased prothrombin gene mutation frequency was found but a significant relationship with thrombosis was identified in the other [23]. In addition, three patients with BD having recurrent venous thrombosis, arterial thrombosis [32] and intracardiac thrombosis [33], associated with the prothrombin G20210A mutation, have been described.

Antiphospholipid antibodies

The frequency of anticardiolipin antibodies in BD varies between 0% and 47% [22,34]. Hull et al. [35] found a significant association between anticardiolipin antibodies and retinal vasculitis, although most reports have found no correlation between these antibodies and vascular events [31,34]. Only three series have studied the prevalence of lupus anticoagulant in BD, with prevalences ranging from 0% to 8% [22,34,36].

Fibrinolysis studies

An activated fibrinolytic process, evidenced by increased levels of plasmin/alpha-2-antiplasmin complexes, has been identified [37,38]. Studies of the components of fibrinolysis are contradictory. Tissue-type plasminogen activator antigen values have been reported as normal or reduced and activity as normal or elevated. Type 1 tissue-type plasminogen activator inhibitor antigen was found to be elevated, and activity normal or elevated. In addition, no relationship has been found in BD between these parameters and thrombosis [27,37,38]. These differences could be due to different methodologies or disease activity status [27]. Finally, normal plasminogen concentrations have been reported in patients with BD.

We recently evaluated all the thrombophilic parameters, thrombin and plasmin generation, endothelial lesion and, for the first time, extrinsic and intrinsic coagulation pathway markers in 38 patients with BD (13 with venous thrombosis). We compared these data with those of 38 patients with unexplained venous thombosis and 100 healthy controls [39]. There were no deficiencies in protein C, protein S, antithrombin, or factor V Leiden in the patients with BD. Homozygous methylenetetrahydrofolate reductase C677T was found in 13% of BD and in 21% of controls. Heterozygous prothrombin gene *G20210A* was found in one BD patient with deep vein thrombosis. Lupus anticoagulant was detected in two BD patients without thrombosis, and anticardiolipin antibodies in one BD patient with venous thrombosis. Compared with control subjects, the BD group had elevated levels of prothrombin fragment 1+2, plasmin/alpha-2-antiplasmin complexes, and thrombomodulin. These levels did not differ between patients with or without thrombosis. Activated factor VII and activated factor XII were not elevated in BD.

In the light of our data, although thrombosis in BD patients may, in a few cases, be associated with thrombophilic factors, these do not seem to explain most thromboses. Our study demonstrates that in BD there is endothelial cell injury, increased thrombin generation independent of activation of factors VII and XII, and increased fibrinolysis unrelated to thrombosis.

Treatment

Treatment is generally symptomatic and individualized, given that controlled studies are not available [40]. The optimal treatment of major vein thrombosis is still controversial. The proposed treatments range from platelet anti-aggregating drugs to anticoagulants. Some authors recommend anticoagulants for major vein thrombosis [5], whereas others suggest their avoidance as they may cause bleeding during the vasculitic process. Anticoagulants alone have

no therapeutic effect on the vasculitic process. Therefore, the current practice is to give steroids with immunosuppresive drugs, particularly azathioprine or cyclophosphamide, in combination with anticoagulant or anti-aggregating drugs. Surgery is indicated for aneurysms whenever feasible, because they can rupture. The operative therapy is resection or exclusion by bypass grafting, but there is a tendency to new aneurysm formation in the graft and operated arteries [6]. Postoperative steroids are recommended to prevent relapses of arterial lesions, with better results if steroids are combined with immunosuppressives [19].

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