Vasculo-Behçet's Disease

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Traditionally described as a triad consisting of recurrent aphthous stomatitis, genital ulcerations and ocular disease, Behçet's disease is now recognized as a multisystem disorder. Its clinical expression may be dominated by mucocutaneous, articular, neurologic, urogenital, intestinal, pulmonary as well as vascular manifestations [1,2]. Although vascular lesions are not listed among the criteria for diagnosis of BD [3], up to 25–35% of patients develop venous or arterial large vessel complications throughout their disease course [2].

There are various types of vascular involvement in BD, and vasculitis is thought to be one of the underlying pathologic processes [4]. The histologic findings show thickening of the media, splitting of the elastic fiber, and perivascular round-cell infiltration. Vascular involvement affects both arteries and veins, and blood vessels of all sizes. Since arterial involvement comprises aneurysm formation and thrombosis, the category of BD in which vascular disease predominates has been termed "vasculo-Behçet's disease." Venous involvement is typified by recurrent venous thrombosis and thrombophlebitis. Not infrequently arterial and venous involvements coexist.

Risk factors for vasculopathy in BD, as well as possible associations of vascular lesions and other systemic manifestations of the disease are still largely unknown. Previously, employing a statistical method of factor analysis, we explored the principle associations between various clinical manifestations of BD in Israeli patients [5]. Factor analysis demonstrated an inverse correlation between superficial venous thrombosis and erythema nodosum, which was more common in male patients. Inverse correlation of these manifestations can partly be explained by the tendency of vascular complications in BD to affect male patients, as stated by Espinosa et al. [6] in their comprehensive review in this issue of *IMAJ*, while erythema nodosum has a clear predilection for female patients [1]. Surprisingly, no association was found between superficial and deep vein thrombosis. This is in contrast to the study of Koc et al. [7], who reported superficial thrombophlebitis as a risk factor for major vein occlusion in BD. Nonetheless, it was also reported that no association existed in the occurrence of superficial and DVT in the general population. It is therefore possible that superficial and DVT might have different pathogenic mechanisms in BD. Another interesting association revealed by factor analysis is the association between DVT and neuro-Behçet. Central nervous system involvement is one of the most serious complications in BD. Neurologic manifestations of neuro-Behçet include brain-stem syndrome, cranial nerve palsies, corticospinal tract disease, meningoencephalitis, seizures, subarachnoid hemorrhage and pseudotumor cerebri [1]. The etiopathogenesis of neuro-Behçet is yet unknown, but intracranial vascular disease – in the form of cerebral venous thrombosis, arterial occlusions and aneurysms – probably plays an important role. Therefore, peripheral deep, but not superficial, thrombophlebitis might be a risk factor for CNS involvement in BD.

As Espinosa et al. [6] extensively discussed, the etiology and pathogenesis of thrombotic events in BD is still obscure. The role of thrombophilic parameters such as protein C, protein S, antiphospholipid antibodies and factor V Leiden have all been analyzed in BD with conflicting results. Vascular endothelial function is impaired in BD. Indeed, anti-endothelial cell antibodies have been detected in sera of patients with BD. Moreover, polymorphonuclear cells of Behçet's patients showed significantly increased adhesion of human vascular endothelial cells compared to PMNs of healthy individuals.

Genetic factors, as yet undefined, might be associated with BD vasculopathy. Indeed we recently pointed to the major role of ethnic origin in clinical expression of BD, including vascular manifestations [8]. We found that Israeli Jewish patients of North African origin have a significantly more severe disease compared to other Jewish ethnic groups, as evidenced by higher rates of various disease manifestations, including ocular disease, arthritis, and neuro-Behçet. Patients of North African origin also had higher rates of DVT as well as overall vascular disease (venous and arterial). Furthermore, we previously showed that Israeli BD patients, who are positive for human leukocyte antigen-B5, have a striking propensity for thrombophlebitis [9]. Increased incidence of vascular thrombosis and superficial thrombophlebitis in HLA-B5 patients was also reported in another study [10], but other investigations showed similar or lower rates of thrombophlebitis in HLA-B5 patients [11]. In view of the great diversity in the clinical expression

BD = Behçet's disease
DVT = deep vein thrombosis
CNS = central nervous system
PMN = polymorphonuclear cells
HLA = human leukocyte antigen

and HLA-correlations reported worldwide, the associations between venous thrombosis and HLA-B5 might be confined to specific geographic areas, and may not necessarily be attributable to other parts of the world. Nonetheless, an association between HLA-B5 and vascular manifestations in BD might explain the low rates of vascular complications in patients from areas with low prevalence of HLA-B5 (e.g., the USA and Northern Europe).

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