

# Vascular Involvement in Behcet's Disease - Vasculo-Behcet

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## INTRODUCTION

The triad of recurrent ulcers in oral and genital mucosa coupled with eye inflammation (uveitis) was first described by Hulusi Behcet in 1937 [1]. Many patients have since been diagnosed with the disease and additional systems and organs were found to be involved such as brain, joints and the digestive system [2,3].

Behcet's disease is found along the Silk Road from eastern Asia (where women are more affected) to the Mediterranean basin with a male predominance of 4 to 1 [2,4]. Turkey has the highest prevalence with 80-370 cases per 100,000 followed by 13.5-20 in Japan and China [5]. The prevalence in the US is only 0.5-7.5 cases per 100,000 [6]. Both genders are affected, mostly at their third and fourth decade of life [7].

The etiology is greatly unknown, but is probably autoimmune in nature, and the onset, typically in the third or fourth decade of life, is followed by relapsing acute inflammations. There is no specific laboratory test or immunologic marker for the disease. There is, however, some genetic predisposition associated with HLA-B51 [8].

Although vascular involvement has a profound effect on the morbidity and mortality in Behcet's disease it has no substantial significance in the differential diagnosis. Thus, it was only recently considered as part of the diagnostic criteria [9]. Under these new criteria 4 points are needed for diagnosis. Ocular lesions, oral aphthosis and genital aphthosis are each assigned 2 points. The pathergy test 1 point as for central nervous system involvement and vascular involvement.

The involvement of the vascular system, which dominates the clinical picture in Behcet's disease, is termed vasculo-Behcet's disease [10]. In vasculo-Behcet there is a male predominance at a ratio of nine to one. Vasculitis is responsible for much of the pathologic process. Arteries and veins of all sizes may be involved. In vasculo-Behcet's the vascular complications dominate the clinical signs and symptoms of the disease making other systems involvement less noticeable and less important with regards to the long-term outcome of patients [10]. Thus, it is prudent to diagnose and treat these patients in order to prevent vascular complications. The most common cause of sudden death is vascular complication [11,12].

At the first visit, only 20% of patients have vascular involvement [6]. Overall, up to 50% of patients have a vascular involvement, mostly young males with 75% of them within five years of the disease onset. Large vessels are affected in 8-40% of all vascular involvement [13-15].

## TYPES OF VASCULAR INVOLVEMENT

There are four types of vascular involvement:

- a) Venous thrombosis. Veins may demonstrate superficial thrombophlebitis (**SVT**) and deep vein thrombosis (**DVT**).
- b) Varicosities and chronic venous insufficiency.
- c) Arterial occlusions. These occlusions may lead to organ infarction and limb loss.
- d) Aneurysms. True aneurysms or pseudoaneurysms may result in rupture and mortality.

In general, venous disease is more common than arterial and may even be an early symptom of the disease. Ample studies reported that patients with Behcet had a fourteen-fold higher risk for thrombosis compared to controls [16]. Major vein thromboses such as superior and inferior vena cava, portal vein, hepatic vein and dural sinuses were reported on, in up to 30% of the patients [12,13,16,17]. However, the most frequent venous involvement is deep vein thrombosis (**DVT**) of the lower extremities. Superficial vein thrombosis (**SVT**) at any site was described as the next common lesion and specifically after venipuncture. Both are accounted for 60-80% of all vascular lesions [18,19] and can be considered as the hallmark of the disease. With SVT one can find a red, hard cord along the course of the affected vein. DVT is presented with swelling and pain while walking. Typically the thrombus is firmly adherent to the vessel wall and thrombosis may progress despite proper anticoagulant treatment [13,18]. Venous wall damage and adventitial inflammation are encountered, biochemical markers, however, are negative [20,22].

Although others have reported that some factors known to cause tendency towards thrombosis (thrombophilia) such as factor II and V show polymorphism in Behcet's disease [21,22].

Unlike in non-Behcet's patients, spontaneous and post-treatment recanalization rates of the inflamed veins are rather low [16,20]. Thus, patients with vasculo-Behcet are more prone to have chronic venous insufficiency with long-standing venous hypertension resulting leading to postphlebotic syndrome. Patients are younger than non-Behcet patients with venous thrombosis [15,16,19]. Lower extremity vein thrombosis may affect simultaneously both legs in 40-60% of the patients [20]. Also, a high cumulative recurrence rate of venous thromboses was noted, reaching 20% at one year and 40% at two years [13,18,19,23].

The second most common site for venous thrombosis is in the vena cava diagnosed in 15% of the patients. Superior vena cava thrombosis results in face and upper body swelling and effort dyspnea (SVC syndrome). Symptoms and signs are exacerbated by bending forward [13]. There seem to be less relapses and the overall prognosis is favorable. Thrombosis of the inferior vena cava, mostly the infra-hepatic segment, or ilio-femoral thrombosis with relapses leads, in turn, to venous claudication in up to a third of the patients [18,23]. The hallmark finding is swelling of the legs and visible abdominal collaterals.

Arteries may be involved in up to 7% of all patients with Behcet and are affected by vasculitis with its perivascular and endovascular inflammatory process resulting in a unique spectrum of stenoses, thrombotic occlusions, bleeding and aneurysms [11,16,18]. Arterial thrombotic occlusions are rather rare [24]. In patients with pulmonary artery involvement approximately a third will demonstrate isolated thrombosis, the majority however, have aneurysms [13]. In sharp contrast to other autoimmune diseases, there is no homogenous wall thickening and the process of atherosclerosis is characteristically not accelerated in patients with Behcet [25].

Aneurysms in Behcet's disease are thought to result from obliterative endarteritis coupled with intense inflammatory process resulting in destruction of the media and fibrous thickening of both intima and adventitia thereby distending the arterial wall [11,18,26]. The pathogenesis of aneurysms in Behcet's syndrome is due to the destructive inflammatory process. Matrix metalloproteinase proteins (**MMP**) and especially MMP-9 may play an important role as was reported on [27]. Aneurysms in Behcet's disease are unique and different from regular aneurysms because they appear at a younger age, approximately seven years after the diagnosis and tend to be more saccular (Figure 1 and 2) compared to the fusiform degenerative aneurysms [11,28].



**Figure 1:** An axial CTA slice demonstrating a saccular abdominal aortic aneurysm.



**Figure 2:** Angiogram showing a saccular abdominal aortic aneurysm.

In addition, Behcet's disease is the only vasculitis causing pulmonary artery aneurysms. Also, there seem to be no real correlation between the diameter of aneurysm and risk for rupture [29].

The abdominal aorta is the most common site for rapidly growing aneurysms accounted for approximately 60% of all arterial involvement in Behcet [30]. Abdominal pain is the leading symptom. Abdominal aortic aneurysms are more commonly involved than the thoracic aorta, followed by pulmonary artery and then various arteries of all sized [13,18,31,32]. Pulmonary

artery aneurysms, notoriously known for bleeding tendency, are characterized by massive hemoptysis, bilateral hilar opacities on images and harbor a 25% mortality rate [13].

Behcet's patients with peripheral aneurysms, such as femoral artery or popliteal artery aneurysms, may present with a painful swelling [33,34].

## TREATMENT

The treatment of venous thrombosis in Behcet's disease is controversial. The mainstay treatment in non-Behcet patients with DVT is anticoagulation. In Behcet's disease anticoagulation is not recommended due to the firm adherence of the thrombus to the venous wall [18]. Immunosuppressive treatment was essential for DVT in patients with Behcet's disease, while anticoagulation deemed not required [35,36]. Immunosuppressive treatment was demonstrated to prevent relapses and prolong survival. Mild doses of steroids may be added to the immunosuppressive treatment for 2-3 weeks to alleviate symptoms. Due to the reported high recurrent rate of DVT, azathioprine should be administered to all the patients and may also prevent superficial thrombophlebitis [37]. For superior vena cava thrombosis diuretics and steroids should be added to azathioprine to ameliorate symptoms. Vena cava filter implementations should be avoided in Behcet's disease due to rarity of thromboembolic events and potential activation of inflammatory response to the puncture.

Treatment of chronic venous insufficiency and postphlebotic syndrome is similar to non-Behcet patients including walking, exercise training, compression stockings and invasive or minimal-invasive intervention for symptomatic cases. Under this treatment regimen the long-term prognosis is usually fair with improvement in more than half the patients regardless of the initial severity [38].

Arterial vascular involvement harbors life or limb threatening situations and thus careful follow up and active treatment is the standard of care, especially when an aneurysm is encountered [28,34]. Aneurysms in Behcet's patients have a grave prognosis because many tend to present with rupture. The usual treatment indications according to size, progression rate and symptoms are not so applicable to Behcet's disease aneurysms due to the fact that most aneurysms are saccular and tend to rupture without correlation to their size [11,18,26]. Open surgery when electively employed should be performed in the remission rather the active phase of the disease [10,32,39].

Due to the fact that Behcet's disease affect both arteries and veins most surgeons prefer to use a synthetic graft [34,45,47], rather than utilizing autologous veins. Anastomoses should be performed only in arterial segment deemed healthy [28,33,40,43,46,48]. Some authors recommend on strengthening by duplication at the anastomotic sites, reinforcement with pladgets and cover with muscle wrapping in the leg or omental wrapping in the abdomen [11,28,39,46,48]. Others justify ligation only, for peripheral aneurysms, especially when dealing with a recurrent pseudoaneurysm [33,41,49].

Pseudoaneurysms (Figure 3 and 4) may develop in the anastomotic sites in 30-50% of the operated cases [46,49,50]. Every repair harbors the notorious risk of a new recurrent pseudoaneurysm. Steroids and immunosuppressive treatment should always be added to the surgical treatment [15,40,51-54].



**Figure 3:** An axial CTA slice showing a right femoral pseudoaneurysm.



**Figure 4:** CTA demonstrating a right femoral pseudoaneurysm after aorto-bi-femoral bypass.

Endovascular treatment is an increasingly widely used modality for the treatment of aneurysms. It is claimed that this treatment modality is preferred in Behcet syndrome due to its minimal trauma to the arterial intimal layer and thereby causing less inflammatory reaction [42-46]. The second advantage when treating abdominal aortic aneurysms is avoiding sutures in the abdomen. Pseudoaneurysms may recur in the groins only where their finding and treatment is easier. Pseudoaneurysms and their recurrence hamper the results of interventional treatment rendering long-term survival outcome of Behcet's patients with arterial involvement to be poor [15,45,52,53]. Follow up every six months is mandatory.

## SUMMARY

Behcet's disease is a unique autoimmune disease of unknown etiology, found along the old Silk Road. It is diagnosed in the third to fourth decade of life and demonstrates relapses. Vascular involvement dominating the clinical pictures is termed vasculo-Behcet where there is a male predominance of nine to one. Arteries and veins of all sizes may be involved. Venous thrombosis tends to be recurrent and the firm adherent to the wall results in poor recanalization. Arterial aneurysms gravely affect the morbidity and mortality of patients with Behcet. Aneurysms are mostly saccular and tend to rupture even without correlation to their diameter. Elective surgical treatment is better during remission. Sutures should be done only in deemed healthy arterial segments. Recurrent pseudoaneurysms are very common. Therefore there seem to be an advantage for endovascular approach. Medical treatment is crucial and necessary for any interventional treatment. Lifelong follow up is warranted.

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