

# Ocular Involvement in Behçet's Disease

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## INTRODUCTION

Behçet's disease (BD) is a multisystem inflammatory vasculitis characterized by mucocutaneous, ocular, vascular and neurological manifestations [1]. There is no specific laboratory or radiological evidence for a disease that is thought to be an autoimmune disease [2]. HLA B51 positivity or positive pathergy test help to diagnose, but they are not required for diagnosis. Different rates of pathergy test positivity have been reported in different geographies in Behçet's disease worldwide [3]. Ocular manifestations are common in BD and can be severe. Ocular involvement in BD includes: anterior uveitis, cataract, glaucoma, posterior segment involvement, vitritis, retinitis, panuveitis, retinal edema, cystoid macular degeneration, venous and arterial occlusions, disc edema and retinal detachment [4,5].

## EPIDEMIOLOGY

The BD is common along the historic Silk Road and in the Mediterranean basin. Overall, the rate of ocular involvement in BD is 50%. In different series this rate is reported between 30-70% [6]. Ocular involvement may result in severe or complete loss of vision [7]. Epidemiologic data are also affected by genetic factors [8]. One study reported that smoking or tobacco use did not increase ocular involvement in BD. The cause is attributed to the effect of nicotine on anti-inflammatory effects, decreased cytokine production, and altered nitric oxide levels [9,10].

## CLINICAL FINDINGS

Patients are generally unaware of ocular involvement at the onset of BD, especially with anterior segment or vitreous involvement. Clinical manifestations may include pain in the eye, globe tenderness, photophobia, epiphora and decreased vision [19].

The most common involvement in BD is uveitis, which means the inflammation of the uvea. Uvea is located in the middle part of the eye. Anterior uvea contains the iris and ciliary body. Posterior part is called choroid. Panuveit is referred to as the presence of concurrent inflammation in the anterior chamber, vitreous humor, retina and choroid.

### Anterior Chamber Involvement

The most characteristic findings at the cellular level are seen in the anterior chamber. The most typical finding is the flare on the inflamed iris veins, which gives a foggy appearance to the anterior segment. Detection of hypopyon is an indication of activation. Hypopyon is an accumulation of dense cellular and fibrinous material in the lower parts of the anterior segment and consists of polymorphonuclear leukocytes, inflammatory material and tissue fragments. It occurs due to gravity. The hypopyon is displaced by the patient's movement or position change [11]. Cellular debris in the anterior vitreous of the eye without any symptoms may be a marker of ocular involvement [12]. Posterior synechiae may develop in the anterior segment. These synechiae are the adhesion of the posterior surface of the iris and the anterior surface of the lens. It causes stiffness and irreversible adhesions in the pupil. Other less common anterior chamber findings are conjunctival aphthae, episcleritis and scleritis redness. Four Behcet's patients with nodular scleritis have also been reported in the literature [13]. In a Turkish study by our study group, it was reported that the mean platelet volume, platelet-lymphocyte ratio, and neutrophil lymphocyte ratio may help to detect anterior uveitis in BD [14].

### Posterior Chamber Involvement

The main findings of the involvement of the posterior segment are haze and cells formed in the vitreous. The cause of the haze in the vitreous is the protein pools in the siliceous body, choroid or retina. Other findings of the posterior segment are related to the retina. Retinal damage will inevitably occur over time if there is involvement in the posterior segment. If vision loss occurs, this is largely due to retinal damage. Retinal artery involvement has more serious consequences than retinal venous involvement. In the analysis of vascular branches in retinal vasculitis, a new imaging method called "fractal analysis" has been tried [15]. Another finding during both acute exacerbations and remission periods is cystoid macular edema. In this condition, which is resistant to treatments, there is a gradual deterioration of vision loss. Hyperemia and edema in the optic disc and papillitis are common posterior segment involvement. Isolated papilledema is often a sign of sagittal sinus thrombosis. In the literature, such a case has been successfully treated with adding topical prednisolone acetate suspension 1%, topical tacrolimus suspension and artificial

tears to oral methylprednisolone and thalidomide [16]. A study from Turkey reported changes in corneal biomechanics associated with recurrent uveitis and / or corticosteroid use [17].

## PROGNOSIS

Those with BD should be under long-term follow-up and treatment. The factors that cause activation are still not fully known, and it is difficult to predict when activation and when remission periods will develop. As reported previously, the visual prognosis is generally worse in younger men (400). In a comparative study of 1990 and 2000 li, it was stated that visual prognosis is gradually improving over the years, possibly linked to innovations in treatments and the addition of immunosuppressive to treatment [18-20]. In a long-term follow-up study of a Saudi Arabian origin, the proportion of patients who worsened gradually in the presence of ocular involvement was found to be 56.5%.

## COMPLICATIONS

Complicated cataracts may develop, possibly due to inflammatory and metabolic changes in the anterior chamber, or the use of corticosteroids. Secondary glaucoma may also develop due to inflammatory mediators and the use of corticosteroids. Depending on the involvement of the posterior segment, epiretinal membrane as well as macular holes may be formed [19].

## TREATMENT

If aggressive treatments are not initiated, especially in young male BD patients, the risk of developing visual loss and even blindness is increasing. Topical, systemic and surgical treatment options are available.

### Topical Therapies

Topical treatments are appropriate and generally sufficient for localized disease to the anterior segment. Treatment of anterior segment involvement has two main purposes. These objectives are to prevent development of mydriasis and to suppress inflammation. For this purpose, tropicamide and cyclopentolate are mainly used topical agents. The application of the adrenaline-dexamethasone mixture to the sub conjunctival area may also be an alternative. The use of topical corticosteroids may also be appropriate. However, it should be kept in mind that long-term use may cause glaucoma and cataracts. In a pilot study, an intravitreal infliximab injection was also attempted and a 20% visual improvement was recorded [21].

### Systemic Therapies

Various immunosuppressive agents may be used in posterior segment involvement, especially with macular involvement and retinal vasculitis. If symptoms cannot be controlled, cyclosporine can be added. Systemic corticosteroids may also be used for rapid suppression of ocular attacks. If there is no response to conventional treatments, biological agents may be added. In placebo-controlled trials, azathioprine has been shown to prevent the frequency of uveitis attacks [22]. TNF

alpha and interferon alpha antagonists are among the options [19]. In a study that lasted nearly 10 years, azathioprine was added to the treatment of pulsed cyclophosphamide and success in ocular manifestations has been shown [23]. In another study, the use of infliximab for 4 years has been shown to reduce the frequency of ocular exacerbations and retinal vascular poundings [24].

## **Surgical Treatment**

In complicated cataracts and glaucoma, surgical treatments can be used [19].

# Vascular Involvement in Behçet's Disease

## INTRODUCTION

The main pathological involvement in Behçet's disease (BD) is vasculitis. There may be involvement in vessels of all sizes (small, medium, large) in the arterial system and venous system. Arterial involvement is most commonly seen in small vessels, but involvement of the middle and large vessels may also be present. The main vascular involvements are arterial occlusions, arterial aneurysms and major venous occlusions. Venous involvement is more common than arterial involvement [25]. Arterial aneurysms are more common than occlusive conditions [26]. The incidence of thrombotic conditions in vascular BD is increased, which is not explained by the inadequacy of thrombotic factors [27,28].

## EPIDEMIOLOGY

In a Turkish study evaluating BD of 2319 BD, the frequency of vascular involvement was reported as 14.3% and it was emphasized that most of the patients were male. The frequency of BD varies between 5% and 40% in the literature [27-30]. The first vascular attack (75%) is usually within the first 5 years after the onset of the disease [29].

## CLINICAL FEATURES AND TYPES OF INVOLVEMENT

Vascular involvement of BD is characterized by inflammation [31,32]. Compared to the other BD manifestations, it tends to start at an earlier age [33]. The most common clinical feature is the involvement of small veins in the lower extremity (70%) [30]. In a survey of 493 BD patients, 53 patients had major venous involvement. Among them, hepatic vein thrombosis was the most common with 14 patients [34]. Venous involvement is more common in BD with positive pathergy test or ocular involvement. The affected veins are femoral vein (superficial, deep and common), popliteal vein, saphen vein (magna and parva) and crural veins according to decreasing frequency [35]. Vascular inflammation is diffuse and usually complicated by thrombus formation [36]. It has been shown that the risk of vascular involvement in BD is also associated with an increased level of anti-C1q antibodies [37]. In another study, angiopoietin-1, an angiogenic mediator, was reported to be significantly lower in BH [38]. In our study we conclude that increased mean platelete volume can predict the risk of Deep venous thrombosis development as well as the male sex among BD patients [39].

On physical examination, the superficial lesions of the lower extremity veins look like a string-like rope. Acute involvement of deep lower extremity veins may result in pain, edema, swelling, casting of leg hair, varicose vein formation, hyperpigmentation, in duration and ulceration [35]. Doppler ultrasonography can also distinguish acute and chronic forms of lower extremities [40].

Vena cava inferior thrombosis can be investigated in 3 anatomic regions: Infra hepatic, hepatic and supra hepatic regions. Although involvement may be present in all regions, infra hepatic involvement is most common. If bilateral common femoral vein thrombosis is present in BD, there is a risk of inferior involvement of vena cava at the frequency of 50% and iliac vein involvement of 20% [35]. Budd-Chiari syndrome can develop as a result of hepatic and supra hepatic vena cava inferior thrombosis [34].

Budd-Chiari syndrome is a complication that may be endemic in countries like Turkey, which is less than 5% of BD vascular involvement. It is a manifestation that develops due to hepatic venous obstruction [41]. Abdominal pain, acid, formation of collateral vessels in the abdominal wall, edema in the scrotum and widespread swelling in the lower extremity characterize the clinical manifestations. In addition, jaundice, encephalopathy, splenomegaly, hypersplenism and esophageal varicose hemorrhage can also be seen. The mortality rate is around 60% and most patients die within the first 10 months after diagnosis [42,43].

Vena cava superior thrombosis is a relatively uncommon manifestation compared to vena cava inferior thrombosis. Dyspnea and edema are the symptoms. The edema can be seen along jugular veins (face and upper extremities). Rarely, it may be accompanied by thrombosis of the superficial veins of the lower extremity. It may cause complications such as hemoptysis, pleural effusion, chylothorax and sleep apnea [27-29].

Cerebral venous sinus thrombosis is a complication that is common in young men and develops shortly after the onset of the disease [29]. It is a common occurrence in children [44] and can lead to pyramidal findings, hemiparesis, behavioral changes and convulsions [30].

Pulmonary artery involvement is a rare form of infiltration less than 5%, but it is the most common clinical form of arterial involvement. Massive hemoptysis resulting from pulmonary artery aneurysm, is a lethal screen with bilateral hilar opacities in the images, accompanied by cough, fever, pleural pain. Most large proximal segments of the pulmonary branches are involved. It has been reported to be seen more frequently in males [45]. Pulmonary embolism is very rare [33].

Cardiac involvement is a very rare form of involvement in BD. Intra cardiac thrombosis, pericarditis, myocarditis, endocarditis, endomyocardial fibrosis, coronary arteritis and valsalva sinus aneurysm may occur [46]. The most common form of cardiac involvement is intra cardiac thrombosis [47]. Coronary artery involvement and insufficiency of the valves are less frequent. It has been reported that intima-media thickness of coronary arteries and coronary artery calcium scoring may be noninvasive markers for assessing cardiovascular risk in BD [48,49].

Vascular involvements and their incidence in BD were summarized in a study of 728 diseases. (Table 1) [50].

**Table 1:** Vascular disease in 728 patients with Behçet's syndrome [51].

	Number of patients
<b>Venous disease</b>	
Deep venous thrombosis	221
Subcutaneous thrombophlebitis	205
Vena cava superior occlusion	122
Vena cava inferior occlusion	93
Cerebral sinus thrombosis	30
Budd-Chiari syndrome	17
Other venous occlusion included subclavian, iliac, portal, renal, innominate, brachiocephalic.	24
<b>Arterial disease</b>	
Pulmonary artery occlusion or aneurysm	36
Aortic aneurysm	17
Extremity arterial occlusion or aneurysm	45
Other arterial occlusion or aneurysm included iliac, subclavian, renal, carotid, cerebral, coronary, innominate, mesenteric, aorta, basilar, splenic.	42
Right ventricular thrombus	2

## PROGNOSIS AND TREATMENT IN VASCULAR DISEASE

Vascular involvement of BD is one of the major causes of mortality and morbidity. In particular, pulmonary artery aneurysm has a high mortality rate and this rate is 25%, and it is very important to make an early diagnosis and to start treatment quickly [50]. Alibaz F and colleagues concluded lower Chronic post-thrombotic syndrome risk and better venous disease-specific quality of life, symptom severity, and venous disability scores in Vascular BD patients compared with the non-BD group. The main treatment of BD vascular involvement is immunosuppressives, systemic corticosteroids, and surgical treatments. Anticoagulant treatments are also successful.

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