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# Ocular lesions in Behçet's disease

## ABSTRACT

Behçet's disease is a rare systemic vasculitis that involves both arteries and veins of various sizes. The main symptoms of the condition are aphthous mouth ulcers and genital ulcers, skin and ocular lesions, neurological disorders, arthritis and gastrointestinal (GI) complications. Ocular manifestations have the greatest impact on the deterioration of patients' quality of life, as they may cause vision loss. The most typical ocular lesion is posterior uveitis. Often ocular involvement may initially be asymptomatic and difficult to diagnose on standard ophthalmic examination. All patients diagnosed with Behçet's disease should have regular check-ups using the latest diagnostic methods. The treatment of patients with Behçet's disease and ocular manifestations requires the cooperation of a rheumatologist and an ophthalmologist to achieve the best results.

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**KEY WORDS: Behçet's disease; uveitis; eye**

## INTRODUCTION

Behçet's disease (BD) is a systemic vasculitis that involves both arteries and veins of various sizes with unknown aetiology. Inflammation can affect any organ. BD is manifested by aphthous mouth ulcers and genital ulcers, skin and ocular lesions, GI lesions, lesions in central nervous system and joint lesions. The first description of this disease was made in ancient times by Hippocrates. However, we owe a more accurate description and name of this disease to two modern doctors. The Greek ophthalmologist Adamantiades described in 1931 the case of a patient with recurrent iritis, hypopyon, thrombophlebitis, oral and genital ulcers and arthritis of the knees. In 1937, Turkish dermatologist Hulusi Behçet described 3 patients with a triad of symptoms: oral and genital ulcers and recurrent iritis. The current name of the disease is derived from his name. BD was also known as Silk Road disease due to the fact that most cases were found in the area between the Far East and the Mediterranean Sea. Currently, due to population migration, BD is found worldwide including single cases described in Poland. Countries with the highest prevalence include Turkey — 20–602 cases per 100,000 inhabitants, Iran 68/100,000 and South Korea 30.2/100,000 [1]. The average prevalence is 0.6–7.2 for Western European countries and 8.6/100,000 in the USA [2]. BD is rare in Poland and only single cases have been described.

## AETIOLOGY

The aetiology of BD is still unclear. The condition is thought to develop due to an autoimmune reaction in genetically predisposed individuals under the influence of environmental and infectious factors [3]. In terms of genetic factors that are most strongly associated with the occurrence of BD is the presence of HLA-51 antigen. Recent studies have described other non-HLA-related genes that increase the risk of BD. The development of BD is influenced by polymorphisms in genes encoding molecules that are responsible for the body's defence system against pathogens, genes encoding cytokines and adhesion molecules [4]. Differences in terms of genes encoding cytokines involved in response to the occurrence of a pathogen in the body can

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cause a slightly altered defence response that will eventually result in the development of BD. The pathogenesis of BD development includes the pattern recognition receptor dysfunction, in particular toll-like receptor dysfunction in monocytes. Moreover, one of the most common abnormalities is neutrophil hyperactivity that manifests itself in excessive oxidative burst, chemotaxis and neutrophil extracellular network (NET) formation [5]. Infections with Streptococcus sanguis, herpes simplex virus, hepatitis virus, parvovirus B19 are considered as possible infectious agents. Researchers are currently looking for the relationship between dysbiosis of the gut microbiome and known genetic factors that predispose to the development of BD. The pathomechanism includes changes in the pathway of short-chain fatty acid production in the gut and mutations in genes involved in regulating this process [6].

## OCULAR LESIONS

Ocular involvement (OI) is the third most common manifestation of BD following dermatological and articular manifestations. OI is particularly dangerous because it can occur bilaterally, rapidly causing visual impairment and disability [7]. In addition to decreased visual acuity, patients may complain of ocular hyperaemia and eye lacrimation, decreased sense of contrast, visual light hyper-sensitivity, loss of depth perception and colour perception, presence of vitreous floaters, and reduced visual field [8]. The lesions that may occur in the eyes include anterior uveitis, cataract, glaucoma, posterior uveitis with vasculitis, vitritis, retinitis, uveitis, retinal oedema, cystoid macular degeneration, retinal artery or vein thrombosis, and retinal detachment [9]. Based on studies conducted in countries with the highest number of cases (Turkey and Japan), both ocular involvement and a higher risk of blindness were observed in men. In the ocular manifestations of BD, lesions are usually bilateral and they occur approximately 2–3 years after the onset of the disease [10]. In approximately 20% of patients, ocular symptoms may develop first [2]. Eiman Abd El Latif et al., in their study involving 681 patients with BD in Egypt, observed that bilateral uveitis was 10-fold more common than unilateral uveitis, and posterior uveal involvement (as isolated posterior uveitis or as a component of uveitis) was 7-fold more common than isolated anterior uveitis [11]. Ocular lesions may be more common than those reported in the literature because some pathologies are difficult to diagnose on a standard slit-lamp ophthalmoscopy or fundus examination. Only more specialised examinations such as fluorescein angiography, near-infrared autofluorescence, indocyanine green angiography and others can prove the presence of typical ocular lesions [12]. In countries with a high prevalence of BD, the risk of vision loss in patients with uveitis is very high. The average time to develop blindness from the onset of first ocular symptoms in Turkey and Japan is 3.36 years. In 50–90% of cases, patients' visual acuity was 20/200 or below after 4 years of the disease. R. Oktay Kaçmaz et al. assessed 168 patients with ocular manifestations of BD and found that significant factors that affected the risk of vision loss were the presence of posterior synechiae, persistence of high-grade intraocular inflammation, elevated intraocular pressure (IOP), and ocular hypotony. Furthermore, active inflammation was found to be associated with an increased risk of ocular complications, and thus effective treatment and control of inflammatory activity are of great importance. It was also observed that cataract, macular oedema and epiretinal membrane were the three most common ocular complications in the population under study [13]. Ocular BD is dominated by non-granulomatous uveitis that may involve the anterior, posterior or bilateral uveae. Inflammation limited only to the anterior uvea is rare (10–15% of cases) and most cases occur in women [14]. Isolated anterior uveitis may resolve spontaneously and lead to anterior synechiae, posterior synechiae, iris atrophy, and hypopyon [15]. Hypopyon develops in 5–30% of patients. The resulting anterior uveitis is most often not associated with fibrinous exudate, an thus inflammatory cells can move freely and contribute to inflammation in other structures of the eye. On this basis, it is possible to distinguish BD-related hypopyon from hypopyon associated with, inter alia, inflammatory spondyloarthropathies. The hypopyon observed in uveitis in inflammatory diseases of the spine contains a large amount of fibrin that makes the inflammatory fluid thick and viscous and prevents the inflammation from spreading to other structures of the eye [16]. Recurrent anterior uveitis may lead to glaucoma. Elevated intraocular pressure occurs as a result of closure of the iridocorneal angle caused by anterior synechiae or as a result of inflammation [17].

However, posterior segment involvement is more common in BD (50–93% of cases) and may include vitritis, retinal vasculitis, retinal vascular occlusion, and cystoid macular oedema [16]. Posterior segment involvement is most closely associated with prognosis of visual loss. If only the posterior segment of eyeball is involved, patients usually complain of painless visual impairment and increased vitreous floaters [15]. A constant symptom in posterior uveitis is diffuse vitritis. Vitreous opacity is greatest at the onset of the inflammatory response and may sometimes lead to blurred fundus images. If the eye fundus is visible, optic disc hyperaemia and optic disc swelling, inflammatory infiltration of the retina, retinal vein occlusion and retinal detachment can often be observed [18]. Retinal vasculitis is the most serious complication of BD that affects the arteries and veins of the posterior segment of eyeball [19]. The appearance of this manifestation is most strongly associated with an increased risk of vision loss. Retinal vasculitis may resolve if treatment is started quickly enough; untreated retinal vasculitis progresses and causes vascular obliteration, necrosis and fibrosis [12]. The most visible retinal lesions include thromboangiitis and necrotising vasculitis that affect both arteries and veins. Swollen veins, vascular sheaths, thickening vessels, intraretinal and vitreous haemorrhage, macular oedema, retinal ischaemia and infarction, optic disc oedema and retinal scarring are then observed. Repeated episodes of vasculitis eventually lead to permanent vascular occlusion, tissue hypoxia, resulting in neovascularization of the disc (NVD) or neovascularization elsewhere (NVE) around the border of ischaemia [15]. Transient superficial retinal infiltrates are pathognomonic of BD, may occur in any number and anywhere, and they resolve without leaving a scar. Another pathognomonic sign is the accumulation of inflammatory deposits on the peripheral retinal surface during resolution of diffuse vitritis [18].

## DIAGNOSIS

Several ocular manifestations of BD can be difficult to diagnose on a standard slit-lamp examination or fundus examination. Recent examinations that are useful in the diagnosis of ocular lesions include laser flare photometry and fluorescein angiography. The latter method is considered the gold standard for monitoring persistent intraocular inflammation, as it is the best method to visualise retinal vascular leakage and the presence of retinal ischaemia [18]. Loss of visual acuity is closely related to posterior pole involvement and the degree of retinal and macular vascular leakage, which is best visualised by fluorescein angiography [20]. Another important examination complementary to angiography is optical coherence tomography that enables imaging of pathologies within the macula flava (macular oedema, retinal cysts, retinal detachment, atrophy of fovea, etc.) [17]. Recent studies are looking for methods for early diagnosis of ocular lesions in BD. Yoo-Ri Chung and Eun Hyung Cho found that the measurement of subfoveal choroidal thickness using enhanced depth imaging optical coherence tomography (EDI-OCT) can be a clinical indicator of subclinical ocular inflammation [21].

## TREATMENT

Treatment of ocular manifestations depends on the site of lesions. For the treatment of anterior uveitis, topical administration of glucocorticosteroid eye drops (mainly dexamethasone) and drugs that dilate the pupil and paralyse ocular accommodation (tropicamide, phenylephrine, atropine) are recommended [7]. According to the 2018 EULAR guidelines, patients with posterior uveitis should be treated with azathioprine, ciclosporin, interferon alpha or anti-TNF-alpha antibodies. Systemic administration of glucocorticosteroids should be used combined with azathioprine or another immunosuppressive drug, only for rapid induction of remission [22]. According to experts' recommendations, all patients with posterior uveal involvement should be treated with azathioprine or ciclosporin (or a combination thereof). In the case of exacerbation of posterior uveal involvement, glucocorticosteroids should be included in the treatment (using gradually decreasing doses, with a maximum duration of glucocorticosteroid therapy of 3 months). When standard therapy fails, biologic drugs should be used — INF-alpha as a drug of first choice and anti-TNF-alpha antibodies as a drug of second choice. In some cases, where the risk of vision loss is very high, biologic drugs should be included as a priority [16]. In terms of TNF inhibitors, infliximab, adalimumab and golimumab have the highest proven efficacy. The inclusion of anti-TNF antibodies in standard therapy often enables redu-

ced doses of immunosuppressants or glucocorticosteroids. In terms of anti-TNF agents, etanercept is ineffective. Other biologic drugs require further evaluation of efficacy on large groups of patients [8]. Intravitreal injections of glucocorticosteroids should only be an adjunctive therapy to general immunosuppressive therapy in patients with involvement of one eye. In patients with anterior uveal involvement and poor prognostic factors such as young age, male sex and appearance of ocular lesions at a young age, immunosuppressants may be considered. However, the evidence for the efficacy of such therapy is limited and this issue requires further research [22].

## CONCLUSIONS

The ocular manifestations of Behçet's disease can cause patients to experience a significant deterioration in their quality of life and is a real threat of vision loss. All patients diagnosed with Behçet's disease should undergo regular eye check-ups using highly specialised examinations, as ocular involvement may be initially asymptomatic. The treatment of patients with BD and ocular complications requires ophthalmologists and rheumatologists to collaborate to achieve a better therapeutic effect, significantly improve patients' quality of life and reduce the risk of vision loss.

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