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REVIEW ARTICLE

# Inflammatory manifestations of herpesviridae infection in the anterior segment of the eye

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## Summary

**Introduction:** *Herpesviridae* is a large family of double-stranded DNA viruses with eight types known to infect humans: Herpes simplex virus (HSV) type 1 and 2, Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein Barr virus (EBV), Human herpesvirus (HHV) 6, 7 and 8. Herpetic eye disease can affect the anterior and/or posterior segment of the eye. In this article we focused on the anterior segment manifestations.

**Methods:** A review of research articles with key words scleritis, keratitis, anterior uveitis, herpetic, HSV, VZV, CMV, and EBV published in PubMed database until April 30th, 2024 was done.

**Results:** HSV1, VZV, and CMV are well known to cause inflammation in the anterior segment of the eye**,** which includes episcleritis, scleritis, keratitis, and anterior uveitis or their combination. However, there are reports of anterior segment inflammation caused by EBV, HSV2, or HHV6. The disease usually has a recurrent or chronic course and persistent inflammation can cause severe damage to the ocular tissues, which can significantly impair vision. Although some types of ocular inflammation can be effectively treated with antiviral agents during active phase of the disease (HSV1, HSV2, VZV, CMV), so far there is no final treatment which would permanently prevent the recurrences. The main complications include corneal scarring, scleral thinning, glaucoma, synechiae, iris atrophy, and cataract.

**Conclusion**: Due to its recurrent or chronic course, the herpetic inflammation of the anterior segment of the eye remains a challenge for clinicians. While typical clinical clues may sometimes lead an ophthalmologist to suspect a herpetic cause of the inflammation, a definitive diagnosis—especially in atypical cases—can only be confirmed by PCR verification of the viral genome from ocular tissues or, in cases of uveitis, by detecting local specific antibody production in the aqueous humor using the Goldmann-Witmer coefficient.

**Key words**: Herpetic eye disease, scleritis, keratitis, anterior uveitis, Herpesviridae, HSV, VZV, CMV

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## INTRODUCTION

*Herpesviridae* represent a large family of ubiquitous viruses with more than 130 subtypes identified. The virion consists of a lipoprotein envelope, tegument, nucleocapsid, and double stranded DNA with up to 200 genes. In this family, eight members can infect humans including: Herpes simplex virus (HSV) type 1 and 2, Varicella zoster virus (VZV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Human herpesvirus (HHV) 6, 7 and 8. All of them, except for HHV-8 have been documented using PCR in samples from ocular tissues or fluids with inflammatory manifestations.

Herpetic eye disease can affect anterior and/or posterior segment of the eye. Anterior segment disease can manifest in many ways such as episcleritis/ scleritis, keratitis, anterior uveitis, or their combination (keratouveitis, sclerokeratitis, sclerouveitis, or sclerokeratouveitis), while posterior manifestations include necrotizing (acute retinal necrosis and posterior outer retinal necrosis) and non-necrotizing retinitis (1).

In this article, authors will focus on the anterior segment manifestations of different members of *Herpesvirdae* family, their epidemiology, clinical presentation, complications, differential diagnosis, and treatment options.

## METHODS

A review of research articles with key words scleritis, keratitis, anterior uveitis, herpetic, HSV, VZV , CMV, EBV published in PubMed database until March 31$^{st}$ 2024 was done. To ensure the most accurate description of the disease's clinical presentation and complications, only clinical studies that confirmed the virus through polymerase chain reaction (PCR) or the detection of specific local antibody production using the Goldmann-Witmer coefficient were included in the review.

## EPIDEMIOLOGY

HSV type 1 is ubiquitous viral agent that usually infects the host by droplet transmission, or less often by direct inoculation. Primary infection typically occurs early in life and is most often asymptomatic, with nearly two-thirds of cases going unrecognized (2). Rarely, primary infection can manifest in the eyelids (blepharitis with vesicles and ulcerations on the eyelids), with or without conjunctivitis. However, inflammation of the cornea in the form of dendritic keratitis, or less commonly disciform keratitis, can occur. The prevalence of HSV1 seropositivity increases in general population with age and was documented in 80-90% of persons above 40 years of age (3,4). After the primary infection the neurotropic HSV 1 enters a dormant phase in the sensory trigeminal ganglion. Later during life, it can be reactivated under the condition of immunosuppression, hormonal changes, exposure to radiation, respiratory infection, psychological stress, etc. (5)

HSV type 2 is a cause of genital herpes and is a sexually transmitted disease. Rarely transmission can also occur during labor from a mother to a child (causing neonatal conjunctivitis), or secretions can be transmitted directly to the eye. The prevalence of HSV2 seropositivity is 10-15% in general population (6).

Primary VZV infection (varicella or chickenpox) is transmitted via contaminated air or in direct contact with infected fluids. It usually infects children and young adults and high seropositivity of 80-90% was documented in unvaccinated young population (7,8). After the primary infection, virus resides in a latent phase in sensory ganglia. The reactivation of VZV infection (shingles) can occur in the corresponding dermatome with herpetic neuralgia and maculopapular rash in the area of branches of the ophthalmic nerve (n, frontalis, n. nasociliaris, n lacrimalis) leading to herpes zoster ophthalmicus (HZO). HZO is typically unilateral and usually occurs in elderly patients. Risk factors for HZO are older age and immunodeficiency conditions (HIV, autoimmune diseases, use of corticosteroid or other immunosuppressive therapy, tissue and organ transplantation, chemotherapy, physical and emotional stress) (9).

EBV or HHV-4 is ubiquitous, B lymphotropic virus with seropositivity in general population of up to 90-95% in adult age (10). The infection occurs via contact with infected saliva or genital secretions. It can manifest as infectious mononucleosis in young adulthood or with mild flu-like symptoms.

CMV or HHV-5 is one of the most common viruses worldwide. The infection occurs during childhood or in adolescence, but can also be transmitted vertically during pregnancy leading to multiple organ malformations in a newborn, including eyes.

Human herpesvirus (HHV) 6 includes two subtypes HHV-6A and 6B. Subtype 6A is more neurovirulent and is associated with neuroinflammatory disease. Subtype 6B (along with HHV-7) can cause exanthema subitum in infants and is transmitted via direct contact. The virus can be reactivated in patients with severe immunosuppression.

HHV-7 often acts together with HHV-6, and the viruses are sometimes referred to by their genus, *Roseolovirus*. Similarly to HHV-6, HHV-7 can cause exanthema subitum. However, primary infection is often asymptomatic, although it can manifest as acute febrile respiratory disease, fever, rash, vomiting, or diarrhea.

HHV-8 similarly to other members of *Herpesviridae* family infects the host early in life, and then becomes latent. It is associated with Kaposi sarcoma and is known to be an oncovirus, associated with tumorigenesis (11).

## PATHOGENESIS

Herpesviridae family belong to neurotrophic viruses with tendency to infect sensory nerves (12). Usually following the acute infection with members of Herpesviridae family (HSV-1, VZV and HHV-6), the virus enters a latent phase in the sensory ganglia of the body and for the ocular tissue it is located in the trigeminal (Gasser's) ganglion (13,14). Later during life if the loss of immunity occurs, the reactivation of the viral infection can affect the corresponding dermatome (often seen in VZV as herpes zoster or shingles or in HSV as localized vesicles on erythematous skin lesions). However, recently HSV-1 latency was documented in corneal tissue as well, challenging the standard pathogenesis hypothesis (15).

## CLINICAL MANIFESTATIONS

Anterior segment manifestations of Herpesviridae infection include: conjunctival and lid manifestations (blepharoconjunctivitis), corneal manifestations (keratitis), scleral manifestations (episcleritis and scleritis) and inflammation of the iris (anterior uveitis).

The symptoms in patients with anterior segment inflammation typically include: mild to moderate pain, ciliary hyperemia, photoaversion, and sometimes blurred vision.

### Blepharoconjunctivitis

#### *HSV-1 blepharoconjunctivitis*

Blepharoconjunctivits is a well-known manifestation of primary infection with HSV-1 and usually occurs in children younger than 5 years of age (16). The main manifestations include cutaneous vesicular eruption on the lids and lid margins, follicular conjunctivitis with watery discharge, and preauricular lymphadenopathy. The lesions are infectious for ten days and spontaneously resolve in 15-20 days. In some rarer cases, blepharoconjunctivitis may recur later during life due to reactivation of latent virus in trigeminal ganglion. The lid skin lesions and follicular conjunctivitis are similar to the primary infection and are infectious for only 2-3 days and last for only a week.

#### *VZV blepharoconjunctivitis*

During the primary infection with VZV in childhood (chickenpox), vesicular skin lesions may occur in the lids, lid margins and can be followed by follicular conjunctivitis and preauricular lymphadenopathy. The lesions spontaneously resolve in one to two weeks (17). The exceptions are immunosuppressed individuals like children on immunosuppressive therapy due to autoimmune conditions such as juvenile idiopathic arthritis or with primary immunodeficiency which may have more severe course and require systemic therapy with acyclovir.

During the reactivation of VZV later in life (HZO), vesicular rash may occur in the area of the innervation of ophthalmic nerve on the upper eyelid, forehead and tip of the nose, and always respects the middle line of the face. If the branch of nasociliary nerve is affected (Hutchinson's sign) there is a high risk of eye involvement with manifestations such as VZV conjunctivitis, or corneal (VZV keratitis), scleral (VZV scleritis) or even intraocular manifestations (more often anterior uveitis or very rarely acute retinal necrosis). It always requires systemic antiviral therapy with acyclovir 800 mg 5 times daily for seven to ten days. Patients with immunodeficiency of any cause may require prolonged therapy. Dermatologist usually prescribes local therapy for vesicular skin changes, since they tend to develop secondary bacterial infection if not treated properly.

### Keratitis

#### *HSV keratitis*

Herpes simplex keratitis is caused by recurrent infection of the cornea with HSV-1 and is the most common infectious cause of corneal ulcers and blindness worldwide, especially in industrialized countries (5,18). The global incidence is 1 to 1.5 million new, 9 million recurrent cases, including 40,000 new cases of monocular significant visual impairment or blindness each year (19,20).

The majority of HSV cases manifest as unilateral, although rare bilateral PCR confirmed cases of keratoconjunctivitis (21), keratitis (22–25), and endothelitis (26) have been reported. However, in a study from the Moorfields Eye Hospital, London conducted between 1973 and 1980, 19% of cases had bilateral presentation (27), while in other studies, the incidence of bilateral involvement was lower (1.3-12%), and risk factors included: congenital immunodeficiency, atopy, autoimmune diseases, rosacea, long-term use of corticosteroids or other immunosuppressive therapies, and organ transplantation (28). Studies have shown that the incidence of bilateral HSV keratitis in children ranges from 3.4 – 26%, and that the recurrence rate during the first year after the initial episode is higher than in adults (29–31).

The classification of herpetic keratitis based on the predominantly affected layer of the cornea is as follows: epithelial, stromal, and endothelial forms.

Epithelial HSV keratitis is typically self-limiting and occurs due to the cytopathogenic effect of the virus on the epithelial corneal cells and subsequent cell death. The most common form is dendritic, which is characterized by an epithelial defect in the form of twigs with terminal buds in which further replication of the virus takes place. If untreated or treated with corticosteroid therapy, they turn into amoeboid or geographic forms that cover a

large area with a stripped epithelial basement membrane. Therapy of epithelial form includes local antiviral therapy (acyclovir 3% ointment 5 times daily, for a maximum of 2 weeks) in order to close the defect, and also to reduce the incidence of recurrence both in the first episode and in each subsequent one. There is a possibility of viral resistance to acyclovir, due to repeated episodes and frequent use of the therapy. Considering that other approved antivirals have the same mode of action (to target the viral DNA polymerase), resistant herpetic keratitis represents a therapeutic challenge (32). A large number of studies have shown that trifluridine is as effective as acyclovir, while ganciclovir has a slightly better effect (33). Nowadays, most ophthalmologists prescribe the oral form of acyclovir for the prevention and treatment of recurrent herpetic keratitis (34). Although the therapeutic effect has been proven individually for both local and oral application of antivirals, there is not enough evidence that the combined application leads to accelerated healing (35,36).

Stromal HSV keratitis occurs with or without an epithelial defect. If the defect is not present, it is considered interstitial keratitis. It is believed to represent a stromal immune response in the absence of active viral replication and may be focal, multifocal, or diffuse in appearance (37,38). If ulceration is present in stromal HSV keratitis, it is considered necrotizing. It is believed that in this form active replication of the virus is present in the stroma (39), which leads to intense inflammation that predisposes to scarring, vascularization of the cornea and in some cases perforation.

Endothelial HSV keratitis is called disciform. It occurs as a result of HSV infection of the endothelium (2). The typical clinical picture is characterized by discoid localized edema of the stroma, with keratic precipitates on the corneal endothelium in its projection, while the surrounding cornea is transparent. Rarely, diffuse and linear forms of stromal edema can be seen. There is no inflammatory reaction in the anterior chamber. Stromal and endothelial keratitis are treated locally and systemically with antivirals, but unlike epithelial forms where corticosteroid therapy is contraindicated, in these forms it is necessary. Corticosteroid therapy is gradually reduced during treatment, until it is discontinued, although in some patients, the minimum dose must be used for a longer period. Such patients become dependent on corticosteroid therapy over time, and are at a risk of developing cataract and glaucoma. Patients who are corticoresponders (those who develop increased intraocular pressure due to corticosteroid therapy) and those with stromal keratitis associated with an ulcerative defect present a particular challenge. In the latter group, the alternative is the application of systemic corticosteroid therapy, instead of local, while in corticoresponders a low-potency corticosteroids such as fluoromethalone are used. In the USA, where only trifluridine and ganciclovir are approved as topical antivirals, oral antivirals are preferred due to the limited stromal penetration and side effects associated with prolonged use. Trifluridine, in particular, may cause allergic conjunctivitis, toxic keratoconjunctivitis, and punctal stenosis (19). For stromal and endothelial forms of HSV keratitis, as well as epithelial relapses, the recommended initial dose of acyclovir of 400mg 5 times per day is suitable, while the maintenance dose is 400mg twice daily.

The diagnosis of HSV keratitis is almost always made based on clinical appearance, while supplementary diagnostics such as epithelial cell culture detection and PCR are rarely used. Decreased corneal sensitivity in unilateral keratitis is important for establishing the diagnosis, although it can also be observed in neurotrophic defects of neurological or neurosurgical cause (compression of nerves by a brain tumor or their damage during surgery), while bilaterally present decreased corneal sensitivity is present in patients with diabetes.

Differential diagnosis of the epithelial form of HSV keratitis includes: Acanthamoeba keratitis, VZV keratitis, EBV keratitis, adenoviral keratitis, Chlamiadia trachomatis keratitis, and bacterial epithelial keratitis when the stroma is not affected. Non-infectious causes that resemble the epithelial form are erosion in healing (primary and recurrent), neurotrophic keratopathy, exposure keratopathy, Thygeson keratitis, and limbal stem cell insufficiency. Neurotrophic keratopathy and persistent epithelial defect can also occur due to frequent episodes of HSV keratitis (metaherpes). Differential diagnosis of stromal forms of HSV keratitis without ulceration includes stromal keratitis caused by syphilis, VZV, EBV, rubella, measles, Cogan's syndrome, Lyme disease, and when ulceration is present any bacterial or fungal agent, acanthamoeba, VZV, chemical injury, autoimmune diseases, and exposure keratopathy. The differential diagnosis of the endothelial form includes keratouveitis, Posner Schlossman syndrome, CMV endothelial keratitis, and corneal graft rejection (19).

Complications of herpetic keratitis occur as a consequence of the evolution of the disease and the applied therapy. The disease has a tendency to recur and in the patients with higher number of previous relapses, there is a greater risk of recurrence (18). The dendritic form of keratitis shows the greatest tendency to relapse (56.3%), followed by the stromal form (29.5%), while in geographic lesions it is less common (9.8%). The persistent dry eye (40) and scarring of the cornea (leucoma) with or without vascularization is formed in the area of repeated stromal inflammation. Other complications include glaucoma and cataracts. Secondary bacterial infections occur in neglected cases, especially where there is no adequate monitoring of the use of corticosteroid drops. The repeated episodes of the stromal form (metaherpes), can lead to corneal perforation requiring tectonic keratoplasty. The success of graft transplantation, whether tectonic or for the purpose of visual rehabilitation in severe leukoma, largely depends on the vascularization of the cornea,

which is a risk for graft rejection, as well as on the relapse of HSV keratitis on the donated tissue (41). In order to prevent the deterioration of the graft, patients who are preparing for transplantation are on oral antivirals for a long period of time (one year) before and after the surgery (acyclovir 400 mg twice daily). It is desirable that the patient does not have a recurrence of HSV keratitis at least one year before the surgery.

### *VZV keratitis*

Herpes zoster ophthalmicus (HZO) represents a set of clinical manifestations on the eye and adnexa that occur as a result of VZV involvement of the ophthalmic branch of the trigeminal nerve (especially the nasociliary nerve which is responsible for the innervation of the ocular structures). In patients with HZO, involvement of the eye is documented in 50% of cases (42) and includes conjunctivitis, episcleritis, keratitis, uveitis, and retinitis.

The typical presentation of HZO is unilateral neuralgia in the area of innervation of the ophthalmic nerve and eruption of vesicles and pustules on the skin of the corresponding dermatome. Eruption of vesicles may be preceded by fever, weakness and headache. The presence of a vesicle on the tip of the nose is called Hutchinson's sign and is a result of involvement of the nasociliary branch of the ophthalmic nerve (43). In immunocompromised patients, the disease can manifest bilaterally. When the eyelids are affected by vesicles, there is often associated blepharitis, episcleritis and conjunctivitis, and due to severe inflammation accompanied by extensive swelling of the eyelids, ptosis of the upper eyelid may be seen.

As with HSV keratitis, the disease can manifest as epithelial or stromal keratitis. The epithelial form manifests as punctate or pseudodendritic keratitis. In the first form, a punctate edematous lesion with positive fluorescein staining are present, and are in fact the site of active viral replication. Pseudodendrites resemble dendritic HSV keratitis, but there is no real defect, no terminal buds, and they stain minimally with fluorescein.

Stromal keratitis can be superficial or deep. It usually develops after the epithelial keratitis. The superficial form, known as nummular due to its distinctive granular appearance, is thought to result from an immune reaction to the virus in the stroma. A month after the acute phase, a deep stromal form of keratitis can develop, which is characterized by pronounced edema. This form can be associated with anterior uveitis. Keratitis can be accompanied by viral trabeculitis, with increased intraocular pressure. Furthermore, the damage of the corneal nerves due to prolonged inflammatory reaction can cause neurotrophic keratopathy. Complications may include dense leucoma and melting of the cornea in the area of neurotrophic keratopathy. Secondary bacterial infections in the setting of unrecognized or poorly controlled keratitis are common.

The diagnosis is made on the basis of the clinical picture, reduced corneal sensitivity, while additional diagnostics (cell culture, PCR) is rarely performed. In patients with bilateral occurrence of HZO or a disseminated form of the disease (multiple dermatome involvement), HIV testing is indicated (43).

Differential diagnosis in different stages of HZO disease include: HSV keratitis and dermatitis, viral, bacterial or allergic conjunctivitis, exposure keratitis, acute glaucoma, infectious and non-infectious ulceration of the cornea, corneal abrasion, impetigo, cellulitis, insect bite, contact dermatitis.

Therapy includes urgent (ideally in the first 72 hours) per oral acyclovir 800mg 5 times a day for 7 days, and then gradual reduction to a maintenance dose of 400 mg twice daily. Valacyclovir 1000mg or famciclovir 500 mg are also given 3 times a day for 7 days. In immunocompromised patients, acyclovir is administered intravenously at 10 mg/kg of body weight every 8 hours for at least 7 days, and foscanet at 90 mg/kg every 12 hours (for patients with acyclovir resistance). Local application of acyclovir has not been shown to be effective as in HSV keratitis (43).

In our clinical practice, it is common to recommend B complex vitamins and vitamin C along with antivirals. Topical antibiotics are used to prevent bacterial infection when keratitis is accompanied by an epithelial defect. Local corticosteroids are used in stromal keratitis, uveitis, trabeculitis, while the systemic use of corticosteroids is contraindicated in HZO due to possible exacerbation of the disease. In patients with increased intraocular pressure, antiglaucoma therapy is required until pressure control is achieved. In USA, the VZV vaccine is recommended for patients over 50 years of age (44,45).

### *EBV keratitis*

EBV keratitis is thought to be mediated by both active viral replication and immunological processes in the corneal tissue (46). Three types of keratitis associated with EBV infection have been reported: subepithelial infiltrates resembling Thygeson's keratitis, bilateral interstitial nummular ring-shaped keratitis in young patients with systemic mononucleosis, and multifocal non-suppurative keratitis involving the full-thickness or deep layers of the peripheral cornea followed by corneal neovascularization (46,47).

## Scleritis and episcleritis

Members of Herpesviridae family, namely HSV and VZV, have been documented in cases of chronic unilateral scleritis and episcleritis. However, they represent a rare cause of scleritis and episcleritis, but unilateral manifestation may be indicative of herpetic cause.

Episcleritis tends to be mild and self-limiting with painless dilatation of episcleral blood vessels, but in

chronic cases may progress to scleritis (48). Scleritis is most commonly chronic non necrotizing, diffuse or nodular, in both HSV(49) and VZV(50,51) cases. However, a necrotizing case of VZV scleritis has been reported (52). Scleritis presents with intensive pain which increases with eye movements, ciliary hyperemia, lacrimation and sometimes chemosis. Herpes zoster ophthalmicus may precede VZV scleritis. They typically respond promptly and completely resolve after therapy with acyclovir and may require long term prophylactic treatment with this drug (400 mg twice daily).

Epstein-Barr virus (EBV) has been documented in cases with salmon-colored conjunctival masses in patients after acute mononucleosis and lymphoproliferative disorders. Furthermore, EBV can cause hemorrhagic conjunctivitis (46). In rare cases, EBV has been documented in patients with chronic progressive nodular necrotizing scleritis (47). Those patients tend to respond to prolonged therapy with valacyclovir.

## Anterior uveitis

Members of Herpesviridae which have been documented in patients with chronic anterior hypertensive uveitis are HSV, VZV and CMV (11,53,54). Some rare cases of EBV anterior uveitis have been documented using PCR of aqueous humor (53).

### *HSV anterior uveitis*

HSV anterior uveitis tends to occur in younger population (between 30 and 50 years of age), and has a recurrent course. During the recurrences patients complain of pain, redness of the affected eye and blurred vision. Clinical signs include unilateral moderate to severe ciliary hyperemia, decreased corneal sensitivity, corneal pathology (such as dendritic or disciform keratitis and endothelitis 25-54%), (55–57) medium to large keratic precipitates (76-100%), (55,58,59) moderate to severe anterior chamber exudation, sometimes hyphaema may occur, and in chronic cases corneal scarring (12-33%), (57,59) sectorial atrophy of the iris stroma (49-71%), (59–61) and iris sphincter atrophy with irregular pupil are present. As complications, posterior synechiae may occur (in 25-41%), (55,58,59) increased intraocular pressure (in 38-86%), (57,61) and cataract (in 15-37%) (58,59).

The main differential diagnosis of anterior granulomatous uveitis includes: tuberculosis, sarcoidosis (62), sympatheitic ophthalmia (63), Voght Koyanagi Harada disease (64), multiple sclerosis, etc. However, herpetic anterior uveitis typically presents unilaterally, whereas other conditions usually manifest bilaterally.

The main complications include glaucoma, corneal opacities, cataract, posteror synechiae, and iris atrophy. Glaucoma is caused by acute trabeculitis or obstruction of trabeculum with inflammatory cells. In rarer chronic cases, glaucoma may be due to posterior synechiae with pupilar block or secondary scarring of the trabeculum (65).

The treatment of anterior uveitis includes administration of topical corticosteroids, cycloplegics and in cases of corneal involvement antivirals (acyclovir 3% ointment). For patients with secondary glaucoma usually antiglaucoma topical therapy along with cautious usage of low potent corticosteroids (like 0.1% fluorometholone) is sufficient for treatment of trabeculitis. Systemic antiviral therapy is mandatory and includes acyclovir 400 mg 5 times daily first one to two weeks with gradual decrease in dose and prolonged therapy with maintenance dose of 400 mg twice daily for at least two months.

### *VZV anterior uveitis*

VZV anterior uveitis occurs most commonly in elder patients (50-70 years of age), often after HZO (immediately or months later). Symptoms are similar as in HSV anterior uveitis except that post-HZO neuralgia may be more severe. Clinical signs include unilateral moderate to severe ciliary hyperemia, extremely decreased corneal sensitivity, corneal pathology (such as pseudodendritic or nummular keratitis and endothelitis (0-20%)) (55,56,61), small to medium size keratic precipitates (70-100%) (56,59) which tend to become pigmented during the course of the disease (60), severe anterior chamber exudation, and sometimes hyphaema may occur, in chronic cases corneal scarring (9%) (57), and sectorial atrophy (10-76%) (55,59,61) of the iris may be seen. As complications, posterior synechiae may occur (in 0-40%), (55,58,66) increased intraocular pressure (in 40-85%) (55,57), and cataract (in 17-35%). (58–60)

The differential diagnosis includes other unilateral anterior uveitides of viral origin, such as HSV, CMV, EBV, and rubella.

The main complications are similar for all Herpetic anterior uveitides and include glaucoma, corneal opacities, cataract, posteror synechiae, and iris atrophy. Glaucoma has the same pathophysiology as in HSV anterior uveitis.

The treatment of anterior uveitis includes topical corticosteroids, cycloplegics and in cases of corneal involvement acyclovir 3% ointment. Glaucoma therapy is similar as for HSV anterior uveitis. Systemic antiviral therapy includes acyclovir 800 mg 5 times daily first week with gradual decrease in dose and prolonged therapy with maintenance dose of 400 mg twice daily.

### *CMV anterior uveitis*

CMV anterior uveitis always has chronic course and has a clinical picture which resembles Fuchs' heterochromic uveitis. It affects adult patients (40-70 years of age). Patients mainly complain of floaters in visual field. Clinical signs include unilateral mild ciliary hyperemia, normal

corneal sensitivity, corneal pathology (such as endotheliitis (0-40%)) (55,56,58), small diffuse stellate keratic precipitates (39-100%) (55,56,58), mild anterior chamber exudation, in chronic cases diffuse iris atrophy (20-50%) (55,56,58) may be seen. The main complications include iris heterochromia, increased intraocular pressure (in 60-100%) (55,56,58), and cataract (in 29-100%) (57,58).

Complications are less severe then for other Herpetic anterior uveitides and include glaucoma, cataract and iris atrophy.

The treatment of anterior uveitis is controversial since there is no final consensus regarding the most effective therapy, and includes topical corticosteroids, cycloplegics, ganciclovir 0,15-2% gel, (67) and even intravitreal ganciclovir injections were reported as effective in long term clinical studies (68). Glaucoma therapy is similar for all Herpetic anterior uveitides. Furthermore, in some clinical studies per oral valganciclovir 900 mg twice daily for two weeks followed by 450 mg twice daily was proposed. However, there was a high rate of recurrence (up to 80%) after the discontinuation of the drug (69).

### *EBV anterior uveitis*

Anterior uveitis is rarely associated with EBV infection and there are only a few PCR-confirmed cases in the literature (70,71). Patients mainly complain of floaters and diminution of vision. Anterior segment manifestations include mild ciliary hyperemia, keratic precipitates which may become pigmented with time, mild anterior chamber exudation, and vitritis which is resistant to therapy. Also, the treatment seems controversial since there is no specific antiviral medication for EBV. Some case series reported that a combination of systemic acyclovir and intravitreal ganciclovir injections may be efficacious in control of intraocular inflammation (71).

### *Other causes of anterior uveitis*

Also, there are rare reports of chronic anterior segment inflammation caused by HSV2 (in young patients, usually granulomatous) (72) and HHV6 (associated with vitritis) (73).

## Investigations

The clinical presentation can often be typical especially in cases with HZO, and for routine praxis can be sufficient to diagnose and treat a patient. However, the only method to precisely diagnose the cause of ocular inflammation is to determine the presence of viral DNA in tissue samples or fluids using the polymerase chain reaction (PCR) or to confirm the local production of antibodies to a certain pathogen using the Goldmann-Witmer coefficient (73).

## CONCLUSION

The herpetic inflammation of the anterior segment of the eye still remains a challenge for the clinician due to the fact that it often has recurrent or chronic course. In some cases, there are typical clinical clues which lead an ophthalmologist to suspect the herpetic cause of the inflammation (chronic unilateral inflammation, typical forms of keratic precipitates, specific pattern of iris atrophy). However, a definitive diagnosis—particularly in atypical cases—can be established only by confirming the viral genome in ocular tissues using PCR or, in cases of uveitis, by detecting local production of antiviral antibodies in the aqueous humor using the Goldmann-Witmer coefficient. The therapy often includes prolonged usage of specific antiviral agents, although there is an increasing number of cases of viral resistance especially of HSV and VZV to acyclovir and CMV to ganciclovir which require alternative medications.

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# ZAPALJENSKE MANIFESTACIJE INFEKCIJE VIRUSIMA HERPESVIRIDAE NA PREDNJEM SEGMENTU OKA

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## Sažetak

**Uvod:** *Herpesviridae* predstvaljaju veliku familiju dvolančanih DNK virusa od kojih osam tipova inficira ljude: Herpes simplex virus (HSV) tip 1 i 2, Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein Barr virus (EBV), Human herpesvirus (HHV) 6, 7 i 8. Herpetična bolest oka može zahvatiti prednji i/ili zadnji segment oka. U ovom radu biće prikazane manifestacije na prednjem segmentu oka.

**Metodologija:** U revijskom radu su analizirani naučni radovi publikovani u PubMed databazi do 30.4.2024. godine sa ključnim rečima: scleritis, keratitis, anterior uveitis, herpetic, HSV, VZV, CMV, EBV.

**Rezultati:** Dobro je poznato da HSV1, VZV i CMV uzrokuju inflamaciju prednjeg segmenta oka**,** i to skleritis, keratitis i prednji uveitis ili njihovu kombinaciju. Ipak, postoje prikazi slučajeva uzrokovanih EBV, HSV2 ili HHV6. Bolest obično ima hronični ili recidivirajući tok i dugotrajna inflamacija može uzrokovati ozbiljna oštećenja tkiva oka, koja mogu značajno oštetiti vid. Iako neki tipovi zapaljenja oka se mogu efikasno lečiti antivirusnim lekovima tokom aktivne faze bolesti (npr. HSV1, HSV2, VZV, CMV), za sada nema finalnog rešenja koje bi trajno sprečilo recidive bolesti. Glavne komplikacije uključuju ožiljke rožnjače, istanjenje sklere, glaukom, sinehije, atrofiju dužice i kataraktu.

**Zaključak**: Usled hroničnog i recidivirajućeg toka bolesti, herpetične zapaljenske manifestacije prednjeg segmenta oka još uvek predstavljaju izazov za kliničara. Iako u nekim slučajevima postoje tipični klinički znaci koji navode oftalmologa da posumnja na herpetični uzrok zapaljenja, finalna dijagnoza (posebno u atipičnim slučajevima) može se postaviti jedino potvrdom virusne DNK iz tkiva oka pomoću PCR metode ili u slučajevima uveitisa detekcijom lokalne produkcije specifičnih antivirusnih antitela u očnoj vodici pomoću Goldman-Vitmerovog koeficijenta.


**Ključne reči**: Herpetična bolest oka, skleritis, keratitis, prednji uveitis, Herpesviridae, HSV, VZV, CMV

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