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Herpetic uveitis: The masquerader

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Abstract
Although a large proportion of anterior uveitis is noninfectious, viruses are regarded as an important cause of infectious anterior uveitis. Herpes viruses are common infectious causes of hypertensive anterior uveitis. PCR analysis of aqueous sample collected at the slit lamp under aseptic conditions for viral DNA is commonly used technique to confirm the diagnosis during the acute phase. Anterior uveitis may be shortened by the prompt use of therapeutic doses of antiviral therapy and maintenance therapy may be effective in decreasing disease recurrence. In eyes with raised IOP, topical antiglaucoma medications can be given. Eyes with severe elevation of IOP may require oral carbonic anhydrase inhibitors, and filtration surgery may be indicated in medically uncontrolled glaucoma with optic neuropathy.
Abbreviations: herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), intraocular pressure (IOP), Keratic precipitates (KPs).

Keywords: Viral uveitis, raised intraocular pressure, angle closure glaucoma

Introduction
Human beings are a natural reservoir for a number of viruses. This may explain the fundamental role of these infectious agents in several diseases, including uveitis. Worldwide, a high seroprevalence of viral infections can be observed. The goal of this article is to highlight viral infections that are common and relevant for the ophthalmologist like herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV).

Discussion
Viral anterior uveitis can occur at any age, but HSV usually presents in the fourth decade, VZV in the sixth decade, and CMV from third up to the ninth decade of life. HSV infection is transmitted by direct skin-to-skin contact. It lies latent within the fifth cranial nerve sensory ganglion and reactivates from time to time, causing recurrent disease. HSV infection may manifest initially in the periocular skin and cornea or may present solely as an acute anterior uveitis [1].
Although a large proportion of anterior uveitis is noninfectious and associated with the HLA-B27 haplotype, viruses are regarded as an important cause of infectious anterior uveitis. Herpes viruses are common infectious causes of hypertensive anterior uveitis [2, 3]. Herpes virus infection in the anterior chamber has been detected in patients diagnosed with Posner–Schlossman syndrome and Fuchs heterochromic iridocyclitis, which were previously believed to be idiopathic [4] Considering that herpes virus induces IOP elevation coinciding with the duration of uveitis, it is assumed that the herpes virus infects TM cells, which are the key cells involved in IOP regulation.
HSV1 keratouveitis is typically unilateral but may be bilateral (18%) and presents acutely with an injected eye and raised intraocular pressure (IOP) in 38%-90% of eyes [5, 6]. HSV (57%-61% of eyes) is associated with dendritic ulcer, disciform keratitis, and interstitial keratitis. Careful observation may reveal the presence of corneal scars in 33% of cases and a reduced corneal sensation [7]. Keratic precipitates (KPs) may be granulomatous or nongranulomatous [7], and the anterior chamber activity is generally moderate with flare and cells. There may be dilated iris blood vessels and segmental iridoplegia with flattening of the pupil. Posterior synechiae may develop in 38% of cases [8]. There may be corectopia or sectoral iris transillumination defects from previous episodes causing iris epithelial or stromal defects in up to 50% of cases [8]. Patchy or sectoral peripupillary iris atrophy is quite suggestive and history of recurrent HSV infections on the lips or genitals can be helpful in narrowing the diagnosis, but they are not always present [9, 10, 11]. Diffuse iris atrophy is uncommon (10% of eyes) [8].

Rarely, HSV has been reported to cause Posner–Schlossman syndrome, Fuchs uveitis syndrome, or acute iris depigmentation and pigmentary glaucoma [12-14]. The inflammation becomes chronic with persistently raised IOP unless specific antiviral therapy is instituted.

Although both HSV-1 and HSV-2 can cause ocular infections such as acute retinal necrosis, HSV-1 is more commonly detected in association with keratouveitis and anterior uveitis than HSV-2 [15].

Prevalence of vitritis in patients suffering from HSV is lesser (43% eyes) [8]. As compared to those with VZV ocular disease. Also these patients tend to have a greater inflammatory response with posterior synechiae, lower incidence of cataract at presentation and lack of chorioretinal scars compared to those having rubella associated uveitis [16].

The IOP of patients in HSV related keratouveitis is usually normal on initial presentation. Patients presenting with elevated IOP generally have recurrent episodes of uveitis. A retrospective study conducted by Falcon and Williams [17]. Showed that patients presenting with elevated IOP had associated keratitis. Another study by Sungur *et al.* of patients with HSV and VZV stromal keratitis, the total incidence of ocular hypertension was 47% during the period of active uveitis and there was a 13% incidence of persistently elevated IOP during the remission period [18]. Van der Lelij [19] *et al*. described anterior uveitis with sectoral iris atrophy in the absence of keratitis. Herpes simplex virus was documented in 83% of these patients and 90% had elevated intra ocular pressure.

Occurrence of glaucoma in patients with HSV uveitis could be due to secondary angle closure due to pupillary block by posterior synechiae or it could be due to increase in aqueous viscocity from elevated proteins, fibrin and inflammatory cells [20, 21]. Damage to the cells within the trabecular meshwork by HSV 1 infection has also been implicated as a possible cause of elevated IOP [22].

Investigations

PCR analysis of aqueous sample collected at the slit lamp under aseptic conditions for viral DNA is the most commonly used technique to confirm the diagnosis during the acute phase. Goldmann-Witmer coefficient, which determines local intraocular antibody production against the virus, taken to be positive when the value exceeds 3, is another useful test that may take up to 2 weeks to become positive in the acute phase, but remains positive in chronic uveitis. In the immunocompromised, PCR is more useful than Goldmann-Witmer coefficient. Combining both tests increases the sensitivity.

Although viral serology may be helpful in excluding a viral etiology when negative, the presence of immunoglobulin G (IgG) is not helpful in confirming the diagnosis as most adults would have had prior exposure to these viruses. A positive IgM indicates concurrent active systemic infection but does not prove ocular infection.

Treatment

Of HSV keratitis has been well studied, and the data suggest that the duration of anterior uveitis may be shortened by the prompt use of therapeutic doses of antiviral therapy and that maintenance therapy may be effective in decreasing disease recurrence [23, 24] Most cases of HSV anterior uveitis are controlled with topical corticosteroids to reduce the anterior segment inflammation, cycloplegics such as cyclopentolate 1% bid to reduce pain and prevent posterior synechiae, and oral Acyclovir 400 mg five times daily for 4 weeks. In severe or recurrent disease, maintenance therapy of Acyclovir 400 mg twice a day is effective in preventing relapse. Alternatively, valacyclovir, which is a prodrug with improved bioavailability, may be used at a dose of 500 mg thrice a day for treatment and 500 mg twice a day for maintenance. Systemic antiviral therapy should be combined with low-dose corticosteroid drops for years, to prevent relapse. In eyes with raised IOP, topical antiglaucoma medications can be given. Eyes with severe elevation of IOP require oral carbonic anhydrase inhibitors, and filtration surgery may be indicated in medically uncontrolled glaucoma with optic neuropathy.

When preparing the eye for surgery, such as cataract removal or filtration surgery, the eye should be quiescent and prophylactic oral antiviral and topical corticosteroids may be beneficial.

Generally, the prognosis of viral anterior uveitis is good if diagnosed correctly and treated with specific antiviral therapy and topical steroids or NSAIDs. Cataract develops in 28%–35% of HSV and 27%-30% of VZV [5, 8]. Glaucoma occurs in 18%–54% of eyes with HSV and 30%-40% of eyes with VZV [5, 8]. An awareness of the presentation of viral anterior uveitis and how to investigate and treat is of paramount importance since missing the diagnosis and treating only with steroids may result in intractable glaucoma, cataract, and loss of vision.

Conclusion

HSV and VZV may present with hypertensive anterior uveitis. Hypertensive anterior uveitis usually presents acutely. HSV presents in the fourth decade, VZV in the sixth decade. Most herpetic ocular involvement is unilateral except for HSV, which may be bilateral. Reduced corneal sensation, scars, and neurotrophic ulcers may be associated with HSV. KPs may be granulomatous or nongranulomatous in HSV and VZV diseases.

Anterior chamber activity may vary from mild to moderate. Posterior synechiae and sector iris atrophy may develop in HSV and VZV anterior uveitis. Vitritis is common in VZV, less frequent in HSV. Cataract and glaucoma are complications common to all herpes viruses.

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Author's Contribution

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