Herpes Simplex Virus: An Important Etiology for Secondary Glaucoma

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HSV: A Basic Introduction

The herpes simplex virus (HSV) is an extremely successful parasite in humans. It typically remains associated with a host throughout life, can achieve sophisticated stages of parasitism, and is one of the most common causes of infection in man. There are 2 distinct serotypes of HSV: HSV type 1 (HSV-1) and type 2 (HSV-2). They are transmitted by direct skin or mucous membrane contact, by venereal routes, or by maternal genital infection to the newborn. HSV-1 classically causes infections above the waist, for example, the eye, nares, or mouth (cold sores); HSV-2 usually causes infections below the waist, for example, the genitals (although in some cases the reverse is true).

The HSV is composed of 4 major components. The core contains double-stranded, linear DNA coiled around proteins arranged in the shape of a barbell. The core is surrounded by an icosahedral capsid that contains 162 capsomeres and measures 100 nm. Lying outside the capsid is the fibrillous tegument. These 3 structures are encased in an envelope composed of nuclear and other cell membranes. The membranes are composed of lipids and proteins. The lipids make the virus susceptible to lipid and ether solvents. Infection causes antigenic changes in the membranes of the cells they infect. Immunologic mechanisms that seek to destroy the virus also act against host cells. The wide variety of proteins in the envelope plays a role in immune responses, serodiagnosis, and disease severity.[1]

HSV can be detected morphologically by intranuclear inclusions and multinucleated giant cells in smears of cells from scrapings fixed in 90% alcohol. Intranuclear inclusions are easily seen with Papanicolaou-stained smears and sometimes with Giemsa-stained smears. Neutralization, complement fixation, passive hemagglutination, complement-mediated cytolysis, indirect immunofluorescent, and enzyme-linked immunosorbent assay can also be used to identify HSV.[1]

■ HSV and Glaucoma: Clinical Presentation

The HSV, type 1, is carried in an inactive state in up to 90% of adults. HSV-1 can cause a wide variety of problems in the eye, including blepharitis, conjunctivitis, keratitis, and uveitis.[2] Actual virus particles have been identified in the human iris,[3] aqueous,[4,5] and cornea.[1] It has also been implicated as a secondary cause of high intraocular pressure (IOP) and glaucoma.

In a retrospective study by Falcon and Williams[6] at the Moorfields Eye Hospital, 50 patients who developed high IOP in association with HSV keratouveitis were studied. The authors believed that glaucoma could be overlooked in a disease process that occurs in an acute, chronic, and intermittent fashion. Moreover, increased IOP as a consequence of prior damage to the trabecular meshwork by HSV keratouveitis could also be overlooked. The patients in the study had suffered from recurrent HSV disease from a few weeks to 30 years before presenting with high IOP. No patients presented with increased IOP at the first manifestation of ocular herpes. In addition, the nature of the first attack of ocular herpes differed from that occurring in association with increased IOP. Patients who presented with their first episode of ocular herpes had either a dendritic or amoeboid ulcer (40%) or stromal disease (60%). Patients with ocular herpes who presented with increased IOP had stromal keratitis (96 to 100%) or a metaherpetic ulcer (4%). None of the patients with increased IOP had just a dendritic or amoeboid ulcer. Most of the patients with stromal keratitis also had an anterior chamber inflammatory reaction. The ocular signs of HSV keratouveitis that presented with increased IOP included the following: disciform keratouveitis (44%), stromal keratouveitis (36%), disciform keratitis (10%), stromal keratitis (4%), scleral keratitis/limbitis (2%), and metaherpetic ulcer (4%). The most striking feature noted by the authors was the preponderance of patients with uveitis in the group who developed increased IOP compared with the group who did not. Gonioscopy examination of the angle could not be performed in the majority of the patients during the acute stage; however, subsequent gonioscopic examinations were normal in all patients. Patients who developed herpetic ocular hypertension suffered an average of 2 attacks during the 4 years of observation. The frequency of ocular hypertension

was greater (2.4 episodes) among patients with irregular stromal keratitis as compared to patients with disciform keratitis (1.8 episodes). The duration of the episodes of increased IOP varied from 1 to 124 weeks with a mean of 8 weeks.

■ HSV and Glaucoma: Pathogenesis

The pathogenesis of HSV keratouveitic glaucoma has been debated. Some authors suggested that increased IOP was not secondary to inflammation, but developed as a result of steroid therapy.[7] Hogan et al[8] performed the first pathologic study of whole, enucleated eyes with absolute glaucoma and herpetic keratouveitis. They showed that severe and widespread alterations in the anterior segment occurred. The epithelium showed diffuse edema, vesicle formation, separation in localized zones from Bowman membrane by fluid, thinning, or ulceration. Chronic inflammatory cells were identified between the epithelial cells and anterior to Bowman membrane. Bowman membrane was frequently absent due to prior ulceration, and was instead replaced by an edematous scar or granulation tissue.

The corneal stroma was noted to be diffusely edematous with some vascularization. There was lamellar separation of the stroma by inflammatory cell-filled fluid. There were some areas of necrosis that contained debris or granulation tissue. The endothelium was edematous and lost in some locations. Lymphocytic keratic precipitates and fibrin were attached to the remaining endothelium or Decemet membrane. The trabecular bands were thick and edematous and a mix of fibrin and chronic inflammatory cells obstructed the outflow channels between the bands. The iris was thickened, edematous, and contained a large number of lymphocytes and plasma cells. Posterior synechia were extensive, and the anterior lens showed signs of cataractous change. The anterior ciliary body also showed signs of chronic inflammation.

Another study by Townsend and Kaufman[9] investigated the pathogenic relationship between HSV and glaucoma in a rabbit model. Thirteen of 36 rabbits (36%) developed increased IOP during the observation period. Initial rises in IOP began 4 to 8 days after infection and coincided with peaks in anterior chamber reaction. In 7 rabbits (11%), decreases in pressure were noted to correspond with resolution of iritis. On histologic examination of the eyes, a diffuse mononuclear cell infiltration of the iris root and trabecular meshwork with disruption of the lamellar arrangement was present. All animals with persistent pressure elevations had anterior synechia and 50% of these animals had retrocorneal membranes covering 180 degrees of the angle circumference. Endothelial cells showed swelling, vacuolization of the cytoplasm, loss of their normally compact arrangement, and large empty patches where necrotic cells has sloughed off without replacement.

These findings suggest that increased IOP in HSV keratouveitic glaucoma is related to trabecular blockade or trabeculitis. Inflammatory cells, fibrin, and plasma proteins may produce a physical blockade of the trabecular meshwork.[8] Retrocorneal membrane obstruction of the angle may also contribute to rises in IOP.[9] Thick and edematous trabecular bands, which may present clinically as limbitis, appears to obstruct trabecular outflow.[8] Posterior synechia formation could cause pupillary blockade and secondary angle-closure glaucoma. However, angle closure was not implicated as a cause of increased IOP in any of the 50 patients studied by Falcon and Williams.[6] The treatment of HSV keratouveitis with topical steroids may increase IOP, as suggested by Thygeson.[6] In contradiction, all patients in another study[5] were noted to have increased IOP before steroid therapy was commenced. The final possibility is preexisting ocular hypertension or glaucoma, which stresses the importance of an awareness of dual mechanisms of disease.

■ HSV and Glaucoma: Management

The management of increased IOP and glaucoma occurring secondary to HSV keratouveitis is directed initially at halting or preventing activation of viral disease. Available antiviral medications in the United States include trifluridine drops (viroptic) and oral antivirals (acyclovir, famiciclovir, and valaciclovir). Trifluridine concentrations have been measured in the aqueous after topical application. Unlike idoxuridine and vidarabine, therapeutic levels of intraocular trifluridine were measured, suggesting a possible benefit in the treatment of deep herpetic disease involving the stroma and iris.[10] After antiviral coverage has been provided, corticosteroids can have a profound and rapid effect on the inflammatory aspects of the disease, in particular the intraocular inflammation with a marked drop in IOP within a few days. With long-term steroid use, the possibility of steroid-induced ocular hypertension should be kept in mind. However, a drop in IOP from steroid suppression of the trabeculitis will precede any steroid-induced pressure rise.[7]

Supplemental antiglaucoma medications may need to be added to adequately control the ocular hypertension. Suggested options include β-blockers, α-agonist, and carbonic anhydrase inhibitors (oral and topical). The IOP usually returns to normal as the intraocular inflammation resolves. Approximately 12% of patients with HSV keratouveitic glaucoma will develop persistent IOP elevation requiring chronic therapy. Filtration surgery may be required occasionally.[6]

The Herpetic Eye Disease Study[11–17] consisted of 5 trials to evaluate the role of steroids and antiviral medications in the treatment and prevention of ocular HSV disease. The findings are summarized in Table 1.

Table 1. *Summary of the Herpetic Eye Disease Study*

1. *Efficacy of oral acyclovir, topical steroids, and trifluridine in treating stromal keratitis* [non-necrotizing (disciform) and necrotizing]—did not improve the number of treatment failures, time to resolution of keratitis, or 6-month best-corrected visual acuity.
2. *Efficacy of topical corticosteroids in treating stromal keratitis*—reduced the risk of persistent or progressive stromal keratitis by 68% and shortened the duration of keratitis.
3. *Efficacy of oral acyclovir in treating iridocyclitis* (trial discontinued due to slow recruitment)—treatment failure occurred in 50% of acyclovir group as compared with 68% of the placebo group (potential benefit, but not statistically significant).
4. *Efficacy of oral acyclovir in preventing stromal keratitis or iritis for epithelial keratitis*—stromal keratitis or iritis developed in 11% of patients in the acyclovir group as compared with 10% in the placebo group (no benefit).
5. *Efficacy of oral acyclovir in preventing recurrent ocular HSV disease*—recurrence rate of 19% in acyclovir treated patients compared with 32% in placebo group. Stromal keratitis subset recurrence rate was 14% (treated) and 28% (placebo). Nonocular HSV recurrence rate was also lowered in the treatment group (19%) compared with the placebo group (36%). No rebound in the rate of disease was seen during the 6 month, posttreatment observation period.
6. *Determinants of recurrent HSV keratitis*—the placebo group from (5) was analyzed. Eighteen percent developed epithelial keratitis and 18% developed stromal keratitis. Prior epithelial keratitis did not significantly affect subsequent risk of epithelial keratitis, but prior stromal keratitis increased the risk for subsequent stromal keratitis by a factor of 10.

■ Is HSV the Cause of Posner-Schlossman Syndrome (Glaucomatocyclitic Crisis)?

In 1947, Posner and Schlossman[18] presented a case series of 9 patients with recurrent attacks of unilateral ocular hypertension with mild cyclitis and few clinical symptoms. Some of the patients were noted to have heterochromia (lighter eye affected) and anisocoria (eye with larger pupil affected). The angles were noted to be open in the 4 patients in whom gonioscopic examination was performed. The attacks lasted from a few hours to 1 month, but rarely over 2 weeks. Visual field changes occurred in only 1 of the patients who had deep cupping of the optic nerve head. Treatment seemed to be of no benefit, so observation was recommended. Surgery was not needed in any of the cases.

Later studies have documented increases in IOP as high as 40 mm Hg.[19–21] An association between Posner-Schlossman syndrome (PSS) and primary open-angle glaucoma (POAG) has been shown, with approximately 45% of Posner-Schlossman syndrome (PSS) patients having concomitant POAG.[22,23]

A recent retrospective study[24] reviewed the clinical course of patients with PSS without coexisting POAG. Fourteen of 53 eyes (26.4%) were

diagnosed with glaucoma as a result of repeated attacks of PSS. The mean age of onset of PSS was 35 years. Those with 10 years or more of PSS had a 2.8 times higher risk of developing glaucoma compared to patients with less than 10-year history duration of PSS. Glaucoma filtering surgery with antimetabolites was performed in 17% of eyes with PSS. They were followed for a mean of 37 months after surgery. Four continued to have episodes of iritis and only 1 had increased IOP during the inflammatory event. The authors believe that glaucoma filtering surgery with antimetabolites can prevent IOP spikes during cyclitic crisis in approximately 80% of cases. The authors also stated that the frequency of attacks and the severity of uveitis was reduced by surgery, as noted by others.[25,26] The functioning filtering bleb may allow inflammatory cells to exit the eye. Hill et al[27] made a similar observation in patients with chronic uveitis who received Molteno implants.

The cause of PSS is unknown, but studies have linked cytomegalovirus and varicella-zoster virus infections to the disease.[28,29] Another study performed by Yamamoto et al[30] examined aqueous humor samples from 3 patients during acute attacks of the syndrome and compared them with aqueous humor samples from patients undergoing cataract surgery. DNA was extracted from all samples and polymerase chain reaction amplification was performed using herpesvirus family primers (HSV, varicella-zoster virus, and cytomegalovirus). All 3 specimens from patients with glaucomatocyclitic crisis were positive for amplified genomic fragments of HSV and negative for varicella-zoster virus and cytomegalovirus. All aqueous humor samples from the controls were negative for all 3 viruses. This suggested that HSV may cause inflammation of the trabecular meshwork and increased IOP in PSS. Although the methods demonstrated that portions of the HSV genome were present, they could not differentiate whether infectious virus was present or the precise location of the HSV DNA in the eye.

■ Is There an Association Between Topical Ocular Hypotensive Therapy and HSV?

Topical β-blockers (timolol),[31,32] prostaglandin F2α analogs (latanoprost),[32–37] and prostamide analogs (bimatoprost)[38] have been implicated in the reactivation of HSV ocular disease in anecdotal human reports[32,33,36,38] and a rabbit model.[31,34,35,37] Symptoms of reactivation include erythema, irritation, foreign body sensation, and blurred vision. Reactivation may also be asymptomatic. Dendrites, ulcers, an anterior chamber reaction, and other signs of ocular HSV may be seen on examination.

Despite these studies, other authors believed that the prevalence of ocular HSV in patients treated with ocular hypotensive therapy is no different than that found in the general population[39] and that a true

scientifically proven causal relationship has not been confirmed.[40] They suggest that case reports lack statistical validity to suggest causation, but may be valuable for signaling potential adverse drug reactions. They also suggest that rabbit model studies rely on unreliable, subjective outcome measures that may not be generalizable to humans.

Studying a rare clinical event, such as ocular hypotensive therapy-induced HSV ocular disease, in a prospective manner would be difficult, if not impossible. A definitive casual relationship has not been determined. However, the anecdotal case reports should not be discounted completely. The addition of topical hypotensive medications, especially prostaglandins, prostamides, and β-blockers, in an eye with known HSV disease may be related to reactivation of the virus and should be recommended with caution.

■ Conclusions

The HSV is capable of causing keratouveitis and secondary glaucoma. Increase IOP is related to trabecular blockade or trabeculitis. Treatment is focused on inhibiting activation of viral disease with antiviral medications. The subsequent addition of corticosteroids may have a profound suppressive effect on the inflammatory aspects of the disease process. Supplemental antiglaucoma medications may need to be added to control the ocular hypertension. Glaucoma filtration surgery is rarely indicated.

PSS (glaucomatocyclitic crisis) also consists of ocular hypertension with cyclitis. The episodes are unilateral and produce few symptoms classically. The cause is unknown, but HSV has been implicated. Approximately 25% of patient with PSS will go on to develop glaucoma, therefore, long-term follow-up is recommended (especially since it occurs in a younger patient population). Antiglaucoma medications can reduce the IOP. However, glaucoma filtration surgery is sometimes indicated and may prevent IOP spikes and reduce the severity and number of attacks.

Finally, ocular hypotensive therapy has been implicated in the reactivation of ocular HSV disease, but this has not been proven in scientific studies. The addition of potentially proinflammatory agents should be used with caution in patients with known ocular HSV disease.

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