

Management and Treatment of Herpes Simplex Keratitis

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Abstract

Herpes simplex virus (HSV) keratitis is a common and serious external ocular infection leading to unilateral blindness, primarily because of its recurrent nature. Despite considerable progress in the understanding of the virus at cellular and molecular levels, there is still a dilemma whether to use antiviral or steroids or both. The risk of using the steroids with its complication has to be weighed against its concomitant risk of progression without it. This dilemma can be reduced to a considerable extent if basic principles of virology and pathogenesis are kept in mind. Therefore, this article reviews current concepts of the virological and clinical aspects of HSV keratitis to enable a broad understanding of the disease process.

Keywords: Herpes simplex; blindness; keratitis

Introduction

Virology

Herpes simplex virus belongs to a family of viruses called Herpesviridae which also includes Varicella zoster virus, Cytomegalovirus and the Epstein-Barr virus. They are composed of a central DNA core and a protein capsid with 162 hollow cylindrical capsomeres. This nucleocapsid is surrounded by an envelope forming a virus particle (virion) with an overall diameter of 130-180 nm.

Virus Types: There are two types of HSV, namely, type 1 and 2. In general, type 1 causes infection above the waist especially eye, mouth and the skin, and type 2, below the waist especially genital herpes, neonatal herpetic keratitis and conjunctivitis.

Viral Strains: The severity and frequency of ocular disease may be influenced by strain differences. Strains

which produce large amounts of glycoproteins are capable of inducing more humoral and cell-mediated immune response [1-3]. These strains may be associated with more severe forms of corneal stromal disease. The viral genome may also play a role in determining the clinical response to topical steroids [4].

Lytic Infection: Herpes simplex virus usually affects tissues of ectodermal origin, such as skin, mucous membrane, or the nervous system. After the attachment to specific receptors on the surface of human cells (adsorption), the virion loses its envelope to the cell membrane and enters the cells by pinocytosis (penetration). The DNA released into the cells travels to the nucleus. There follows an eclipse period during which no virus can be detected. In fact the viral DNA induces the production of both host and virus-specific enzymes, namely, thymidine kinase and DNA polymerase. Viral proteins synthesized in the cytoplasm are transferred to the nucleus where the nucleocapsid is assembled. The nucleocapsids gain an envelope as they bud through the

nuclear membrane. The host cell becomes packed with newly formed infectious particles ultimately undergoing cell lysis and release.

Latency and reactivation: Like other herpes viruses HSV has the ability to induce latent infection. HSV can become latent in the trigeminal ganglia of the host after the primary infection. After the primary infection, the virus enters the sensory nerve endings of that site. The HSV does not produce viral proteins during this time and the viral genome stays at this site. The most important site of the virus latency is trigeminal ganglia. The latency is maintained by Latency associated transcript.

Virus particles travel centripetally to the neuronal cell body by retrograde axoplasmic flow. They can survive here for decades probably integrated into the host-cell nuclear DNA; yet they leave the cell morphologically, antigenically, and functionally normal. This latent infection can be demonstrated by removing the host tissue and culturing it in vitro for several days. It is possible to identify the virus once again. The virus remains latent in most individuals throughout life. But in some people, certain trigger factors such as fever, systemic illness, stress, UV light or general anesthesia may reactivate the virus. The reactivated virus may travel down a nerve independent of the original portal of entry to cause peripheral disease.

Recently it has been suggested that the cornea may be an extra-neuronal site of latent infection. The exact molecular mechanisms involved in HSV latency and reactivation are unknown. Latency-associated transcripts (LAT) have been identified in human and animal experiments. But latency-associated proteins have yet to be identified during latency in vivo. The cornea itself is a site of persistent infection; therefore, injudicious use of topical steroids in chronic disease may promote proliferation and penetration of virus within the cornea. For the same reason considerable care must be taken while selecting patients with corneal opacification for treatment with phototherapeutic keratectomy.

Clinical Features

Primary infection

Primary ocular herpes is considered to be an infection with no previous history. It can develop at any age although most cases occur within the first few years of life, i.e. after disappearance of the maternal antibodies. Salivary contamination from a person with silent salivary shedding of herpes labialis is the most common source of

infection. Aphthous stomatitis is the usual clinical picture, which can range from subclinical to very severe infection. However primary HSV infection can also occur in other mucous membranes, including the conjunctiva.

Primary ocular HSV infection most commonly manifests as blepharoconjunctivitis which is predominantly unilateral. The periorbital skin can develop intense blisters associated with conjunctivitis and blepharitis. Extensive spread on the facial skin can occur, particularly in eczematous individuals.

The conjunctivitis is usually follicular although severe cases may develop pseudo-membranous reaction. Preauricular lymphadenopathy often accompanies the conjunctivitis. Keratitis develops a few days after conjunctival involvement in 30-50% of cases. The morphology of the corneal lesions varies from superficial punctate keratitis, micro dendrites to frank dendritic ulceration. Stromal involvement is a rare phenomenon.

Diagnosis

The clinical appearance is usually highly suggestive of HSV infection. Also, a history of exposure to a person with active herpes labialis infection may be obtained.

Recurrent infection: The major factors which dictate the severity of recurrent herpes are: immune response of the host, the viral strain, nutrition and treatment. Superficial corneal lesions (dendritic and geographic ulcers) are associated with the presence of replicating virus. Deeper lesions (stromal, uveal) appear to be predominantly due to the immune response.

Corneal epithelial disease: The vast majority of cases of HSV keratitis are those which present with a corneal epithelial lesion, usually a dendritic ulcer. Such individuals may experience this first episode in adulthood. This is due to reactivation of a latent virus from a previously unrecognized primary ocular infection or from a virus which has reached ophthalmic neurons in the trigeminal ganglion during primary infection of the oropharynx. It usually occurs as isolated lesion(s) without involvement of conjunctiva and eye lids. The presenting symptoms include irritation, watering, photophobia, and occasionally, blurring of vision. Cold sores are common in such individuals but are rarely simultaneous.

The morphology of the lesions is quite varied. They can appear as superficial punctate keratitis, stellate epithelial lesions, dendritic or geographic ulcers. Ulcers are usually single but may be several. The infected epithelial cells

appear as opaque lesions which form white plaques. Further enlargement results in dendritic ulceration. The mechanism for dendrite formation is not known, but is thought to be related to linear spread of virus from cell to cell in a contiguous manner [5,6]. With further growth of the dendrite the central epithelium is sloughed off and the lesion stains with fluorescein. The marginal infected cells take up rose Bengal stain. The linear branches characteristically end in expansions called "terminal bulbs". The stroma under the ulcer may show a faint haze and there may be evidence of mild iritis. Corneal sensation is lost in the areas where lesions are present. Repeated attacks may result in generalized corneal anesthesia. In our clinical experience we have noted that recurrent lesions tend to occur at the same site.

Typical lesions involve the central cornea. Ulcers at the periphery of the cornea may behave differently, sometimes masquerading as ulceration due to staphylococcal infection [7]. They appear to have more stromal complications and is more resistant to the treatment [8]. They are also predisposed to chronic trophic ulceration. In a majority of patients, healing occurs with minimal stromal scarring. Repeated attacks and severe infections may result in stromal scarring, thinning and neo-vascularization.

Stromal keratitis: Sight-threatening problems associated with HSV type 1 infection appear to be largely due to an inflammatory response involving the corneal stroma. It is predominantly immune-mediated although in few cases direct invasion and active replication of the virus play a role. Secondary stromal inflammation can follow epithelial or endothelial involvement.

Immune-mediated stromal keratitis is the most common form of the stromal disease where an antibody response is mounted against the viral antigen present in the stroma expressed as a result of persistent infection. There is deposition of antigen-antibody-complement in the stroma. Animal studies [9] show additional mechanisms involved in the stromal tissue destruction. It is proposed that CD4+ T cells play a significant role in the recognition of antigens presented by Langerhan's cells which migrate from limbus to central cornea after HSV type 1 infection. The activated CD4+ T cells release cytokines, interleukin 2 and gamma interferon. Both factors attract large numbers of polymorphonuclear leucocytes which are responsible for corneal tissue destruction.

Clinically there is stromal infiltration without necrosis and ulceration. The size and the area involved may vary

and include small infiltrates to large area of stromal haze. Some cases may be associated with dendritic lesions demonstrating the presence of the entire virus. The outcomes of these lesions vary considerably. Progression or persistence of inflammation can occur. Neovascularization, secondary lipid keratopathy, thinning of the cornea and recurrent inflammation are well recognized. Another distinct form of stromal infiltrate is the immune ring of Weseley. This represents a circular deposit of antigen-antibody complexes with polymorphonuclear leucocyte infiltrate as a result of complement activation [10].

Necrotizing stromal keratitis is typically associated with ulceration. It can follow epithelial disease, superficial stromal disease or disciform keratitis. It is believed to be due to active viral replication and intense immune stromal inflammation. It may be generalized or localized. These cases may have to be differentiated from other forms of microbial keratitis and indeed secondary infection with bacteria and fungi can complicate HSV stromal keratitis. Secondary complications include hypopyon, uveitis, posterior synechiae, glaucoma, retrocorneal membrane, cataract, and rarely, perforation.

Traditionally disciform keratitis (*vide infra*) has been described under stromal keratitis. However, the recent trend is to describe it under endotheliitis as the actual mechanism involved is thought to be endothelial cell infection by HSV with associated inflammation.

Indolent Ulceration: Development of persistent epithelial defects or recurrent epithelial erosions can be seen with HSV epithelial infection. These are generally round or ovoid ulcers with a grey and thickened margin due to piled up epithelial cells. The mechanism appears to be damage of the underlying basement membrane at the time of epithelial infection and denervation. Consequently, the epithelium fails to adhere to the basement membrane resulting in persistent defect or recurrent erosion[11]. Additional factors like lack of trophic innervation, drug toxicity and stromal inflammation may play a significant role. The base of the ulcer stains with both rose Bengal and fluorescein but the viral cultures are usually negative. Persistent ulcers have the potential to progress resulting in corneal melt, perforation, and superinfection [12].

Indolent ulcers (sometimes referred to as "metaherpetic") have to be differentiated from geographic ulcers, which are characteristically caused by inappropriate steroid use. The latter have flat edges and stain with rose Bengal stain. They also change shape due

to continued viral progression. Viral cultures will be positive.

HSV endotheliitis: Progressive or nonprogressive forms of endothelial inflammation can occur with type 1 HSV infection. Dendritic ulceration can precede these lesions in some patients. Disc form keratitis is the most common form. There is a disc-shaped area of stromal oedema occurs without infiltration or vascularization. The area of involvement may be diffuse and central, or eccentric. The presenting symptoms include increased tear production, photophobia, discomfort or blurred vision. A history of herpetic eye disease is usually present. The involved cornea shows appreciable thickening of all the layers with epithelial oedema and folds in Descemet's membrane. Careful examination usually reveals keratic precipitates (KPs) in the affected area, associated with mild anterior chamber activity. Spontaneous clearing can follow although progression to necrotizing keratitis, vascularization, scarring and thinning is also possible. Delayed hypersensitivity mediated by T lymphocytes is probably important in the pathogenesis of disc form keratitis [13,14]. The distribution of KPs strictly confined to the endothelium behind the swollen area suggests cell-mediated reaction directed at HSV determinants on the surface of endothelial cells [15].

Rarely linear involvement of the endothelium can occur. [16,17] In these cases stromal oedema is seen associated with KPs separating the involved and uninvolved cornea similar to the Khodadoust line of corneal graft rejection. Slit lamp examination may show dark areas in the endothelium which appear as non-reflective black endothelial areas under a specular microscope [18]. There may be progression of the endothelial line and the associated stromal oedema. Immunological studies on the aqueous aspirates have revealed HSV antigen in several of these cases [19].

Occasionally diffuse involvement of the endothelium can occur resulting in generalized corneal edema associated with scattered KPs.

HSV iridocyclitis: All deeper forms of HSK can be associated with uveitis. However recurrent non granulomatous anterior uveitis may be an isolated manifestation of HSV ocular involvement occurring without a prior history of ocular HSV infection. Immunological reaction was thought to be the most important cause. Live viruses have been demonstrated in the anterior chamber [20,21] and in the iris tissue [22] in some cases.

Clinically, the severity can vary from mild to severe inflammation resulting in fibrin formation, hypopyon, hyphema, posterior synechiae, segmental iris necrosis similar to the picture seen in zoster keratouveitis, and inflammatory membrane in the angle of the anterior chamber with secondary glaucoma. The recent tendency to treat severe forms of anterior segment involvement with oral acyclovir is best reserved for those cases confirmed by laboratory diagnosis, as dosages and duration of treatment have not yet been defined. [Figure1]

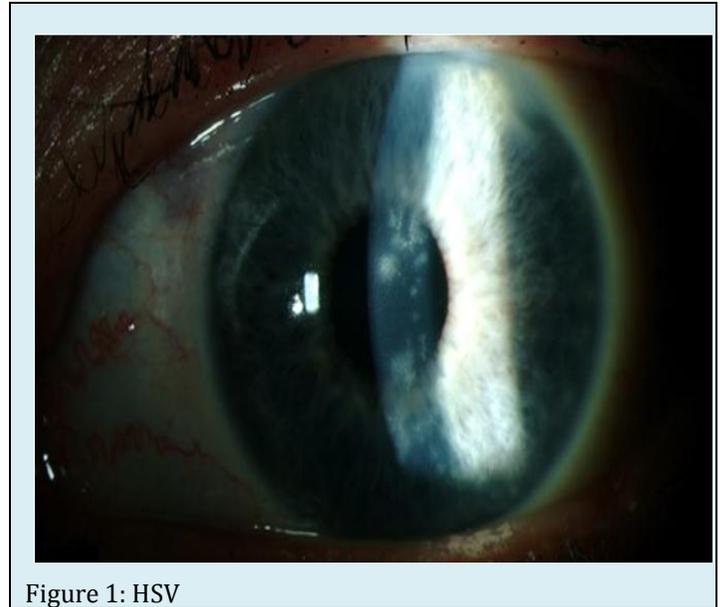


Figure 1: HSV

Trabeculitis: Herpetic peripheral corneal involvement may extend to the trabecular meshwork resulting in trabeculitis. The resultant secondary glaucoma may be transient or lead to permanent damage.

AIDS and HSK: The experience of HSK in post-transplant immuno-suppressed patients suggests that the condition may be more common and more serious than in immunocompetent individuals. An initial report [23] suggested that HSK may be similarly influenced in patients with AIDS. However, the numbers of cases were limited and no control group was used. More recently Hodge and Margolis [24] undertook a larger carefully constructed and controlled retrospective study and concluded that HSK in patients with AIDS and AIDS-related complex was no different in incidence or response to treatment than in a non-immuno-compromised control group of hospital-based patients. Nevertheless, overall recurrence rates were significantly higher amongst the HIV-positive group. If it is assumed that after a first

episode of HSV infection, a site of chronic latent infection is established in the cornea. It suggests that the immunosuppression by HIV infection may impair those mechanisms which are normally responsible for containing such an infection in the cornea.

Laboratory diagnosis: Laboratory tests are not an absolute requisite for the diagnosis of HSV infection as clinical features are often highly characteristic. However, we believe whenever possible, culture should be undertaken to establish a firm diagnosis. The available methods include virus culture, immunological assay and histopathological examination of keratoplasty specimens showing granulomatous reaction in deep stroma and around Descemet's membrane. The common immunological assays to be followed are enzyme linked immune adsorbent assay (ELISA), immune filtration test, latex agglutination, immune peroxidase methods and immune affinity membrane test. Immunocytochemistry may demonstrate HSV antigens in stromal keratocytes, endothelial, and epitheloid cells.

Treatment

Treatment of HSV keratitis and the prevention of recurrences is still a challenge. The main focus for the treatment of herpes simplex Keratitis is to arrest the progression of complication, mainly stromal damage and scarring. The commonly implicated agent to treat HSV Keratitis includes trifluridine, idoxuridine, vidarabine, acyclovir and ganciclovir. Antiviral therapy is the cornerstone for the treatment of HSV keratitis and is still the gold standard [25]. The antiviral agents can be used topically or given orally, oral antiviral having less direct ocular complications. Trifluridine and acyclovir has shown to be more superior to idoxuridine and vidarabine [26]. In terms of ointment, ganciclovir is found to have superior healing rates and better tolerated as compared with acyclovir. Ganciclovir have fewer local side effects such as decreased incidences of burning or blurred vision [27]. Interferon monotherapy is found to be effective against the dendritic epithelial keratitis, but with no added benefit as compared to the antiviral drug mentioned above. The effectiveness of typical antiviral drug can be increased in combination with interferon. The combination of antiviral drug and debridement have better outcome in some patients [28].

The use of steroid in HSV keratitis still possesses a difficult question to the clinicians due to its concomitant side effect profile. Steroids have no added benefit and are

associated with complications and increased recurrences. [29] Topical acyclovir is proved to be more effective than steroid, with fewer episodes of recurrences in the acyclovir group as compared to the steroid. Similarly, corneal epithelial disease had a faster and better recovery with acyclovir [30].

Surgery and Recent Advancements

Conjunctival flap covering surgery is the newer approach for effective treatment of HSV necrotizing stromal keratitis. Conjunctival flap covering surgery with traditional antiviral agents and corticosteroid is shown to be effective in HSV necrotizing stromal keratitis [31]. Deep anterior lamellar keratoplasty (DALK) is an alternate surgical procedure in recurrent HSV keratitis with profound corneal scarring. DALK with peri-operative antiviral prophylaxis is found to prevent the recurrence in this group of patients [32].

Amniotic membrane transplantation (AMT) is another recent development for ulcerative HSV Keratitis treatments. The mice model has shown a new ray of hope in the treatments of HSV ulceration. AMT helps in epithelial lining formation and decreases stromal inflammation and ulcer [33]. The AMT improves the ulcerative HSV Keratitis by local effects with T-cell interference [34]. The use of cyclosporin with acyclovir is a matter of new debate. It has shown to reduce stromal inflammation and haze in HSK keratitis in the animal model [35]. It might be as effective as topical acyclovir but the conclusive results for its use await further clinical trial to access its efficacy [36].

Conclusion

Despite many years of shared clinical experience and understanding, it could be argued that we have made a limited progress in managing HSV infection. We still rely heavily on clinical signs for the diagnosis. We have recognized several influential host factors including the fact that HSK is more common in men than women. We are still not absolutely sure, if the epidemiology of HSK is changing significantly. We have understood the ability of HSV to establish latent infection in sensory neurons and possibly cornea. But we are not yet able to use this knowledge to prevent the disease progression. Acknowledging our limitations may further stimulate application of laboratory knowledge in coping with HSK, which continues to present a major challenge in terms of management.

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