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MINI REVIEW

Herpes simplex virus in the eye

The herpes simplex virus (HSV) remains a significant ocular pathogen despite the existence of highly specific antiviral agents. The clinical spectrum of recrudescent ocular disease induced by HSV involves predominantly the anterior segment and includes HSV shedding in the tear film in the absence of disease; dendritic ulcers (epithelial disease); stromal keratitis with overlying epithelial disease; and stromal keratitis with underlying endothelial disease (disciform keratitis). In addition HSV has been implicated in scleritis and uveitis. HSV is also one of many viruses which have been linked to multiple sclerosis. It is postulated that the viruses have a shared epitope with myelin binding protein.

HSV and varicella zoster virus are the pathogens most commonly detected in the acute retinal necrosis syndrome (ARN). Some similarities exist between ARN and the retinitis induced by cytomegalovirus (another member of the herpes group) in AIDS patients. ARN has also been described in AIDS patients. ARN was reviewed recently by Duker and Blumenkrantz.[1]

It is uncommon for ophthalmologists to see primary HSV disease which may be manifest as a follicular conjunctivitis. Suspicion of a primary HSV infection is confirmed by rising titres of antibodies to HSV. Primary and recrudescent HSV infections can be treated successfully by antiviral agents, the most specific of which is acyclovir. Despite the widespread use of antiviral agents it is extremely rare for clinical isolates of HSV to exhibit resistance.[2]

In anterior segment disease delay in treatment, frequent recurrences, and mistreatment can all result in visual impairment. It is the author's clinical impression that mistreatment with steroids by primary care physicians is becoming increasingly rare. The immunological response to HSV is generally protective for the body. However in the localised context of the cornea an immunological response is often detrimental to its function leading to scarring. The complex response to HSV involving many arms of the immune system has been comprehensively reviewed by Pepose.[3] Corticosteroids may lead to an increased duration of herpetic disease by interrupting the immune system but it is unlikely that they induce viral reactivation. A prolonged corneal infection may be a factor in the genesis of possible latent infections within the cornea. Since the first report of HSV being isolated from human corneas with herpes simplex keratitis after organ culture,[4] evidence has accumulated from human and animal studies suggesting that the cornea may be capable of harbouring latent HSV infections (reviewed by Cook and Hill[5]). If a latent infection can be maintained in a non-neuronal site, then reactivation from a latently infected cornea is likely to be clinically indistinguishable from HSV reactivation in a neuronal site with a subsequent corneal recrudescence. HSV DNA sequences have been detected in a small number of human corneas with no past history of herpetic eye disease.[6 7]

These HSV sequences may be only fragments of DNA incapable of reactivation, but the presence of HSV DNA in 'normal' corneas has important implications for transplantation. Tullo *et al*[8] described the isolation of HSV in the organ culture medium of a corneoscleral disc from a corneal donor. One further HSV isolate has been obtained from another corneal donor in the same laboratory (A B Tullo, personal communication). Neither cornea was used in transplantation.

Reduced visual acuity as a consequence of herpes simplex keratitis remains one of the commonest indications for corneal transplantation in the UK. Between 1987 and 1991 10·5% of 3200 transplants supplied through UKTSSA were performed because of herpes simplex keratitis (A Vail, UKTSSA, personal communication). A study from the Moorfields Corneal Clinic suggests that the expected long term survival for first transplants in quiescent corneas with herpes simplex keratitis is 70%.[9] Earlier studies from the same clinic reported 45% long term survival.[10 11] The improvement in graft survival was aided by prompt removal of loose sutures, concurrent antiviral treatment with immunosuppression during rejection episodes, and prompt treatment of recrudescent HSV disease.

Although the HSV genome has been completely sequenced and is known to contain 70 genes, many of the genes are uncharacterised by structure or function. Different HSV strains show varying degrees of neurovirulence, corneal disease, and reactivation frequency. Specifically engineered HSV mutants with defects in isolated genes are providing valuable information in the biological functions of HSV in laboratory and animal studies. However the greatest enigma in the study of HSV remains the relationship between the virus and the host cell during latency and reactivation, reviewed by Garcia-Blanco and Cullen.[12]

In the HSV lytic cycle the virion carries a protein in its tegument that transactivates its own immediate early genes. This initiates sequential expression of immediate early, early, and late genes culminating in the production of new HSV virions and the destruction of the host cell. The tegument protein mediates this transactivation in association with two cellular factors.[13] Studies suggest that the tegument protein is non-functional in neural cells.[14] This may be because a cellular factor is lacking in neurons,[15] or because neurons express a protein inhibiting the function of the tegument protein.[16] The result may be that the lytic cycle aborts and a latent infection is established.

During latency infectious HSV is undetectable within the host cell. The only detectable mRNAs are the latency associated transcripts (LATs) first described by Stevens *et al*.[17] No protein encoded by LATs has been detected in vivo, although an antigen encoded by LATs has been detected in latently infected neuronal cell cultures.[18] LATs are not essential for the establishment and maintenance of latency.[19-21]

Clinicians are familiar with the concept of trigger factors for HSV reactivation. Many diverse stimuli can induce reactivation and a final common pathway is likely. LATs may play a role in reactivation. LAT mutants have been shown to reactivate less efficiently in vivo.[21] The downstream end of the LAT gene overlaps with the downstream end of an immediate early gene, ICP0. The two genes run in opposite orientations. ICP0 is an important regulatory gene; it transactivates itself; it regulates early and late gene expression and it is important in reactivation.

Although education, specific antiviral agents, and refinements in surgical technique have improved the prognosis for patients with herpes simplex keratitis the condition persists. More than 80% of the community have antibodies against herpes simplex virus. Current treatment options are only

effective in eliminating replicating virus or suppressing an immune response to viral antigens. As yet no therapy has been devised to block reactivation. Such a therapy may also be impractical for prophylaxis given the often long intervals between recurrent episodes of disease. Vaccination may yet be the answer to the prevention of primary HSV infections with subsequent recrudescent disease, but given that HSV has devised the strategy of latency to avoid the immune system, developing an appropriate vaccine represents a considerable challenge.

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