EDITORIAL

Herpes simplex keratitis

Human herpesvirus type 1 or herpes simplex virus type 1 (HSV-1) belongs to the herpesviridae family, six members of which (human herpesviruses 1–6) have been linked to human ocular disease. HSV-1 is a large DNA enveloped virus, with a diameter 150–200 nm, comprising an internal core (containing a genome with *c.* 70 open reading frames), a surrounding icosahedral protein capsid, a tegument and an outer envelope.

Epidemiology and transmission

HSV-1 is the most common infective cause of blindness in many developed countries, with an incidence of keratitis between 5.9 and 20.7 episodes/100 000 person years [1, 2]. Ocular infections occurring for the first time in an individual may represent a primary infection, or a new anatomic site within a previously infected host. Involvement of the lids, conjunctiva and superficial cornea are the most common manifestations of primary ocular herpes.

It is difficult to assess the incidence of primary ocular herpes as it is not known what percentage are asymptomatic and because the diagnosis requires evidence of seroconversion. Even this latter point may be debatable as HSV-1 antibody may be found in the tear film of seronegative individuals [3]. Among children, the incidence of primary ocular herpes ranges between 1 in 8000–1 in 24 000 and 1 in 3500–1 in 30 000 based on the assumption that this is likely to represent the child's first encounter with the virus [1, 4]. In general, primary ocular herpes parallels the incidence of oral herpes, where the peak age of acquisition is before the age of 3 years among the lower socio-economic groups.

Most of the morbidity associated with ocular herpes lies in its ability to recur. This usually manifests clinically as corneal ulceration or a stromal keratitis – herpes simplex keratitis (HSK) – or both. Recurrence rates vary from 9.6% at 1 year, 22.9–33% at 2 years after two episodes, 40% at 5 years, to 67% at 7 years [1, 2, 4, 5]. The rate of recurrence increases in direct proportion to the number of episodes. Each recurrence leads to further corneal scarring and vascularisation, which increases the risk of corneal graft rejection. Furthermore, patients who have had corneal transplantation, are still at risk of further recurrences.

Entry of HSV into the host

Virus replication probably occurs at the site of inoculation, which ensures contact with and entry into the sensory nerve endings. This also results in the production of neutralising antibodies. It may be equally important for HSV-1 to multiply in the ganglion before the immune system has responded, although evidence suggests that control of multiplication by class 1 restricted CD8⁺ cytotoxic T lymphocytes decreases spread into the brain stem [6]. In mice, T cells tend to persist and γ -interferon appears to be expressed after the establishment of latency [7], possibly in response to low level expression of 'immediate-early' HSV proteins during latency [7–9].

Neuronal spread of HSV

HSV is transported within the axon by axoplasmic flow, at a rate of 2–20 mm/h [10] towards the CNS [11], where the virus may interact with the cell nucleus [12] to establish latent or productive infection. Within the trigeminal ganglion, infection is largely restricted to neurones, with little intraganglionic spread to other neurones [10], although this may be possible [13]. Virus transported centrally reaches the nerve root where it may leave the axon to infect astrocytes and oligodendroglial cells [11]. Infection of such cells may then allow virus to enter contiguous axons leading to 'zosteriform' spread [11]. This may explain why the exact site of primary and recurrent disease can differ. It is probable that virus is transported as a non-infectious nucleocapsid and is enveloped in the distal axon [14].

Latency

The determination of which tissues harbour latent virus is important for understanding the pathogenesis of recurrent disease. The trigeminal ganglion is known to contain latent virus. During latency, the latency-associated transcripts (LATs) appear to be the only transcripts expressed, although there are very low levels of 'immediate-early' gene expression [8, 9]. Marker studies [15] indicate that defective viral genomes may also reside in human ganglion cells. LATs are abundant in latently infected human, rabbit and murine trigeminal ganglia and the number of neurones expressing LAT per genome is far higher in

the trigeminal ganglion than in the brain stem [16, 17]. LATs do not appear to be necessary for the establishment or maintenance of latency, but are necessary for efficient viral reactivation [18]. LAT transcription is enhanced in both neuronal and non-neuronal cells by the LAT promoter binding factor [19]. Possibly suboptimal 'immediate-early' expression [8, 9] due to inefficient promoter function results in latency and LAT expression [7–9].

Corneal latency

The cornea is a possible site for harbouring latent virus [20]. Viral antigens have been demonstrated in corneal discs taken from patients with previous HSK and HSV-1 has been isolated from the cornea of 12–29.4% of patients with previous HSK at transplantation [20].

HSV DNA has also been found in the corneas of patients with previous herpetic keratitis [21, 22], apparently non-herpetic corneal disease [21–23] and in eye bank corneas unsuitable or not used for transplantation [23, 24]. The significance of persistent HSV DNA in the cornea is unclear although it suggests that asymptomatic and unrecognised herpetic infections of the cornea are more common than realised. Corneal and neuronal cells regulate the LAT promoter in a similar manner [25] and the finding of LAT transcripts in the absence of glycoprotein gC transcription [22] provides further evidence for the possibility of corneal latency. The limited transcription observed may represent defective genomes [12, 15]. Attempts to detect HSV-1 LATs by in-situ hybridisation in the human cornea have so far failed. Whether this represents a difference in sensitivity between in-situ hybridisation and PCR is not known.

How virus reaches the eye: back or front door?

The frequent occurrence of asymptomatic salivary shedding of HSV-1 [26] implicates the mouth as the main site for the acquisition and spread of HSV-1 within the community. Asymptomatic shedding of HSV in the tear film appears to be much less common [26]. Tullo *et al.* [27] suggested the idea of a 'backdoor' route to ocular disease. Following lower lip inoculation of the mouse, HSV has been recovered from all three divisions of the trigeminal ganglion [27], which suggests that after an oral infection, HSV can establish a latent infection in ophthalmic neurones via the CNS. However, Baringer and Griffith [28] found that lesions are restricted to the ophthalmic division of the trigeminal nerve, following inoculation of the rabbit cornea. Furthermore, HSV has not been recovered from the cornea or tear film after lower lip inoculation of the mouse.

Asymptomatic primary herpetic eye disease may be important in the development of recurrent corneal disease. The frequent detection of HSV DNA in diseased and some non-diseased (eye bank) corneas [20–24] is consistent with the occurrence of asymptomatic or unrecognised HSV-1 ocular infection. Furthermore, the finding of secretory anti-HSV-1 antibody in the tear film of individuals who do not have serum anti-HSV antibody [3], also suggests that the eye may be a primary portal of entry for HSV and that spread beyond the eye need not necessarily occur.

In mice, droplet spread of HSV to the eye in titres similar to those found in saliva results in disease similar to that of primary ocular herpes [29]. In addition, HSV can be isolated from the trigeminal ganglion and iris, and HSV DNA can be found in these tissues as well as the cornea [29]. This supports the idea that HSV-1 can spread into the cornea, iris and trigeminal ganglion, after topical application of virus to the eye. This non-traumatic acquisition of virus by the mouse eye suggests that asymptomatic primary infection in man may lead to a latent infection of the trigeminal ganglion and possibly of the iris and cornea.

As with lower lip inoculation, it has yet to be established whether virus presented by this route can be reactivated in the trigeminal ganglion, iris and cornea to produce recurrent disease.

As HSV cannot be eradicated from the latent state and ocular recurrences cannot be prevented, primary prevention is the main approach to herpetic disease of the eye. The question of whether virus introduced directly into the eye by droplet spread is more or less able to produce recurrent eye disease than virus acquired through the mouth is crucial to this strategy.

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