Commentary: Herpes keratitis: A diagnostic challenge

Herpes keratitis is one of the major causes of infectious blindness in the developed countries. It has been estimated that nearly 500,000 people in the USA are affected with ocular herpes simplex virus 1 (HSV1).[1] The impact of the disease in developing nations is not well established. A study conducted by Kaul *et al*. in North India estimated the incidence of HSV1 as 33.3%.[2] Conventionally, the diagnosis of HSV keratitis is based on a history of recurrent keratitis, as well as typical clinical manifestations in the infected eye.[3] However because of overlapping clinical features with other microbial keratitis and lack of a standardized and practical diagnostic modality, the disease still remains a diagnostic and therapeutic challenge to the ophthalmologists.

After initial ocular infestation, HSV1 can establish latent infection in the trigeminal ganglia for the lifetime of the host. In a study HSV-1 DNA was found in 93% of human trigeminal ganglia.[4] Asymptomatic viral shedding has been demonstrated in tears of healthy individuals in various studies.[5,6] Thus, latency is not absolute because viral replication denoting the production of infectious virus can be missed by the available detection methods due to their very limited sensitivity.[7] The establishment of HSV-1 latency in nonneuronal cells like corneal cells remains an area of controversy.[4,7] Whether cornea acts as a reservoir for HSV1 or just a transient site along the exit pathway from the ganglion is yet to be proven, but there have been reports of transplanted corneas transmitting HSV-1.[8,9]

Virus isolation, though considered a 'gold standard' for diagnosis of viral infections, is time-consuming, has low sensitivity, and requires a special laboratory for viral processing. One of the reasons for the low sensitivity of cell cultures is the fragility of infectious HSV1. The lipid envelope is easily disrupted and thus renders the virus noninfectious and unable to replicate in cell cultures. Electron microscopy can be used to physically observe viral structures, but has unknown sensitivity, is subject to sampling errors, and provides no information on infectivity. Immunofluorescence techniques carry a high rate of false-positive and false-negative results apart from being influenced by subjective variation in the interpretation of data.[4,7]

Polymerase chain reaction (PCR) has emerged as a rapid and reliable tool for diagnosing viral keratitis. Real-time PCR is a modification of PCR which is carried out in a closed system. Unlike conventional PCR it does not require postamplification sample manipulation making it much faster and convenient. Multiplex PCR allows for simultaneous amplification of multiple target sequences in a single tube using specific primer sets in combination with probes labeled with spectrally distinct fluorophores. In contrast, in conventional singleplex PCR, a single target is amplified in a single reaction tube. Multiplexing allows one to distinguish between each PCR amplicon and simultaneously measure expression levels of multiple target sequences of interest. Satpathy *et al*. evaluated the role of PCR in suspected viral keratitis patients in corneal scrapings and tear fluid.[10] They compared the results with virus isolation and Immunofluorescence assay. PCR was found to be much more sensitive than the other two modalities and the detection rate with corneal scraping was significantly higher than tear fluid. Although, the PCR positivity in corneal scrapings was only 36.6%. Ma *et al*. reported the results of RT-PCR in diagnosing viral necrotizing keratitis.[11] They found a viral positivity rate of 46.4% in corneal epithelial scrapings. Fukuda *et al*. studied RT-PCR in tear fluid in all variants of HSV keratitis.[12] They reported highest number of copies of HSV-DNA in herpetic epithelial keratitis followed by active stromal keratitis and persistent epithelial defect. Their detection rate was higher at 88.1% for epithelial keratitis and 59.1% for stromal

keratitis. Guda *et al*. the authors have reported significantly higher positivity with the multiplex RT-PCR as compared to immunofluorescence assay (IFA) and conventional PCR.[13] The study emphasizes the role of multiplex RT-PCR for the detection of HSV and varicella zoster (VZV) DNA in corneal scrapings of suspected herpes keratitis in an ocular microbiology laboratory.

Over the years immense research has been done studying herpes keratitis, but it still remains an enigma in the field of ophthalmology. PCR acts as a powerful adjunct in diagnosing viral keratitis, but a careful history taking and an eye for catching the clinical features are simply indispensable.

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