Progress in Retinal and Eye Research 32 (2013) 88–101

Contents lists available at SciVerse ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Herpes keratitis

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ARTICLE INFO

Article history:
Available online 27 August 2012

Keywords:
Cornea
Keratitis
Herpes simplex virus-1

ABSTRACT

Herpes simplex virus-1 (HSV-1) infects the majority of the world's population. These infections are often asymptomatic, but ocular HSV-1 infections cause multiple pathologies with perhaps the most destructive being herpes stromal keratitis (HSK). HSK lesions, which are immunoinflammatory in nature, can recur throughout life and often cause progressive corneal scaring resulting in visual impairment. Current treatment involves broad local immunosuppression with topical steroids along with antiviral coverage. Unfortunately, the immunopathologic mechanisms defined in animal models of HSK have not yet translated into improved therapy. Herein, we review the clinical epidemiology and pathology of the disease and summarize the large amount of basic research regarding the immunopathology of HSK. We examine the role of the innate and adaptive immune system in the clearance of virus and the destruction of the normal corneal architecture that is typical of HSK. Our goal is to define current knowledge of the pathogenic mechanisms and recurrent nature of HSK and identify areas that require further study.

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[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Alexander Rowe: 35%; S. Jeon: 25%; A. St. Leger: 30%; Knickelbein, Dhaliwal and Hendricks combined contributed the remaining portion of the text and figures. Dr. Hendricks supervised all this work.

1350-9462/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.preteyeres.2012.08.002

1. Herpetic infection

1.1. Types of herpetic disease

Herpes simplex virus (HSV) is a prevalent viral pathogen infecting the majority of world's population. While oral and genital lesions are the most common manifestations of infection, HSV type 1 (HSV-1) can also cause disease in all of the major ocular tissues, including the lids, conjunctiva, cornea, uveal tract, and retina. HSV-1 infection can be categorized into primary and recurrent disease. Following initial primary infection of the oral facial region including the cornea, the virus travels to the innervating trigeminal ganglia (TG) where it establishes a state of latency in which viral DNA is maintained within neuronal nuclei but no infectious virus particles are produced. Thereafter, the virus may undergo cycles of reactivation causing recurrent viral or immune pathology at the initial site of infection.

1.2. Epidemiology

Recent studies show an HSV-1 seroprevalence of >50%, >75% and >90% in the general adult populations of the United States, Germany and Tanzania respectively (Rabenau et al., 2002; Xu et al., 2006). Thus, the majority of the world's population has been infected with HSV-1 and likely carries a latent viral load. Clinical manifestations of primary ocular HSV-1 infections tend to manifest in youths or young adults. Long term studies of ocular HSV-1 in the United States and Britain found the mean age for the first occurrence to be 37.4 years of age and 25 years of age respectively (Darougar et al., 1978; Liesegang, 1988, 1989). The annual incidence of all types of new ocular HSV infections has recently been estimated at 11.8 per 100,000 people in the United States (Young et al., 2010), similar to the incidence of 8.4 per 100,000 people found over two decades ago in a similar population (Liesegang et al., 1989). In France, the incidence of herpetic keratitis was estimated at 31.5 per 100,000 person-years, with 13.2 per 100,000 being new cases and 18.3 per 100,000 being recurrences (Labetoulle et al., 2005). Epithelial dendritic lesions represented the most frequent type of recurrent keratitis (56.3%), followed by herpes stromal keratitis (29.5%), and geographic epithelial lesions (9.8%) (Labetoulle et al., 2005). In the Herpetic Eye Disease Study, herpes stromal keratitis (HSK) represented 44% of recurrences with 18% of patients diagnosed with HSV-1 ocular disease experiencing a recurrence involving the corneal stroma (1998; Liesegang, 2001; Mikloska et al., 2001). Furthermore, previous bouts of HSK significantly increased the risk of future recurrences. Therefore, HSK represents a significant burden of ocular disease caused by HSV-1 infection.

1.3. Clinical symptoms

Clinical manifestations of primary ocular HSV-1 infections are rare and usually occur early in life. They typically present as conjunctivitis that can involve inflammation of the eyelids (blepharoconjunctivitis), marked by inflammatory vesicles and ulcers, and can include dendritic lesions in the corneal epithelium (Darougar et al., 1985). More often HSV-1 ocular infections result from reactivation of virus that originally established a latent infection in the TG following a non-ocular route of infection. Reactivation of latent virus in the ophthalmic branch of the TG can result in shedding at the corneal surface (Shimeld et al., 1990a, 1990b). HSV-1 corneal lesions can either be restricted to the corneal epithelium, a disease referred to as infectious epithelial keratitis (Darougar et al., 1985), or have stromal involvement with or without damage to the overlying epithelium, known as HSK.

Patients with epithelial keratitis may present with pain, photophobia, blurred vision, tearing, and redness (Jones, 1958). Epithelial lesions are caused by the virus replicating in and destroying epithelial cells (Liesegang, 1999). The lesions start as punctuate vesicular eruptions in the corneal epithelium, but quickly coalesce into dendritic shaped lesions (Chang and Dreyer, 1996; Green and Pavan-Langston, 2006). The shape of the epithelial lesion is visualized by staining the basement membrane with fluorescein dye or staining the damaged cells at the outer limits of the lesion with rose bengal dye (Chodosh et al., 1992; Spencer and Hayes, 1970). The lesions can progress to enlarged non-linear lesions referred to as geographic lesions. These lesions can be distinguished from the neurotrophic keratopathy that can develop in patients with recurrent herpes infectious epithelial keratitis by virtue of the swollen epithelial cells and scalloped borders at the margins of herpetic lesions. Because herpetic epithelial lesions are caused by viral cytopathic effect, the lesions can be self-limiting (i.e., controlled by innate and/or adaptive immunity), but heal more rapidly when treated with antiviral drugs, such as trifluorothymidine (TFT) and acyclovir (ACV) (Pavan-Langston and Foster, 1977; Porter et al., 1990).

HSK may occur as a progression from infectious epithelial keratitis, or can be the primary manifestation of keratitis (Knickelbein et al., 2009a). Clinical signs of HSK include stromal opacity, edema, and neovascularization that are triggered by recurrent bouts of HSV-1 reactivation and shedding into the cornea (Fukuda et al., 2008; Kumaraguru et al., 1999; Ohashi et al., 1991) (Fig. 1). The direct effect of the virus, and more importantly, the potent immune response to the viral proteins trigger ingrowth of blood vessels, infiltration of leukocytes, and damage to the corneal stroma and endothelium that combine to promote corneal opacity and edema. The inflammation clears, usually aided by topical corticosteroids, but often with some degree of scar tissue deposition (Jones, 1958; Wilhelmus, 1987). Repeated bouts of HSK can lead to progressive irreversible corneal scarring and blindness.

HSK is often subdivided into two clinical categories: necrotizing and non-necrotizing disease. In necrotizing HSK, an epithelial defect overlies the stromal opacity, and active viral replication as well as immune-mediated tissue damage are thought to contribute to corneal injury (Holland and Schwartz, 1999; Liesegang, 1999). Necrotizing HSK is an eye-threatening emergency requiring aggressive management to prevent corneal melting and perforation. Non-necrotizing, also referred to as immune HSK involves stromal inflammation without an associated epithelial defect (Wilhelmus,

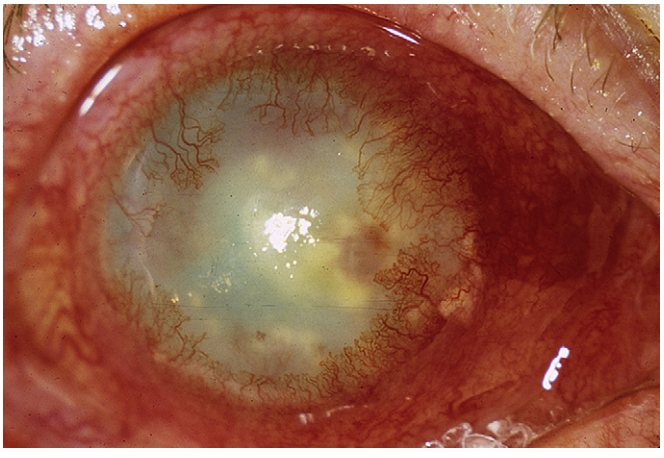

Fig. 1. Slit lamp photograph of a patient with herpes stromal keratitis demonstrating opacity and neovascularization of the cornea.