Chapter 13
Herpes Simplex Virus

Rachel Gordon and Stephen Tyring

13.1 Introduction

Our understanding of human herpes simplex virus (HSV) has increased tremendously since the early descriptions of disease provided by Hippocrates [1, 2]. Notable advances include the correlation of herpetic lesions with genital infections in the eighteenth century [3] and Vidal's recognition of human-to-human transmission in 1893 [2]. Antigenic differences between HSV subtypes, suspected on clinical observations by Lipschitz [4], were confirmed in 1968 [5]. In modern day, there is successful antiviral treatment available for most HSV infections [6]. Insight into the viral life cycle and gene expression has been a driving force behind the development of antiviral treatment, including new vaccines and gene therapy [4].

13.2 Background

Transmission of HSV occurs when a mucosal surface or abraded skin in a seronegative individual comes into contact with virus. Viral replication at the site of primary infection is followed by retrograde axonal transportation of a virion to the dorsal ganglion cells where latency is established by another episode of viral replication [12]. Recurrent infections occur randomly, but there is a positive correlation with

R. Gordon, M.D. (✉)
Department of Dermatology, The University of Texas Medical School at Houston, 6655 Travis Street, Suite 600, Houston, TX 77030, USA
e-mail: Rachel.gordon@gmail.com

S. Tyring, M.D., Ph.D., M.B.A.
Department of Dermatology, The University of Texas at Houston, Houston, TX, USA
e-mail: styring@ccstexas.com

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stress, immunosuppression, UV light, fever, and tissue damage [4, 7]. The severity of the initial infection correlates with the chance of recurrence. Rarely, life-threatening infections occur in cases of severe immune compromise, pregnancy, and neonatal disseminated HSV. "Primary infections" are considered first-time events, but their occurrence in seropositive individuals indicates that latent infection can be established without prior symptoms [6].

HSV infections are ubiquitous, even in remote areas [8]. More than 57 % of the US population between the ages of 14 and 49 are seropositive for HSV1 [9]. Incidence correlates with age in a linear fashion, globally reaching 60–90 % in older adults [10]. HSV1 is most commonly transmitted in childhood and adolescence. The overall incidence of HSV1 is significantly higher than that of HSV2 [10], which occurs more commonly in women and in subpopulations with high-risk sexual behavior [4, 10]. Humans are the only reservoir for HSV infection, and there have been no reported animal vectors [4].

13.3 Clinical Presentation

13.3.1 Oropharyngeal and Orolabial HSV

Infections around the mouth are the most common sites and reservoirs of HSV. Primary infection is usually asymptomatic [11]. Symptomatic cases may include extensive orolabial vesiculo-ulcerative lesions, gingivostomatitis, fever, and localized lymphadenopathy [4]. Adolescents can present with acute pharyngitis and mononucleosis-like symptoms [12, 13]. Dehydration from poor oral intake is the most frequent reason for hospitalization [6].

The incubation period for HSV infections is 4 days on average, and clinical symptoms may persist for 2–3 weeks [4, 14]. Vesicles form within 1–2 days of prodromal symptoms, progress to ulcers in another 1–2 days, and heal within 8–10 days. Pain is most severe with the appearance of lesions [15]. The frequency of recurrences varies among individuals [4], but is estimated to occur in 20–40 % of adults [6], most commonly on the vermillion border. Viral shedding increases with active lesions [16], during episodes of the common cold, oral trauma, and false prodromes [17]. Shedding persists in the absence of symptoms in an estimated 7 % of the healthy population [18] (Figs. 13.1 and 13.2).

13.3.2 HSV Keratoconjunctivitis

Keratoconjunctivitis acquired during birth is usually caused by HSV2. Outside the neonatal period, it is usually caused by HSV1 [4]. These infections result in corneal scarring and vision loss [19] and are the second most common cause of corneal blindness in America [4]. Primary infections can be unilateral or bilateral. Presenting symptoms of pain, tearing, chemosis, and photophobia [6] are associated with

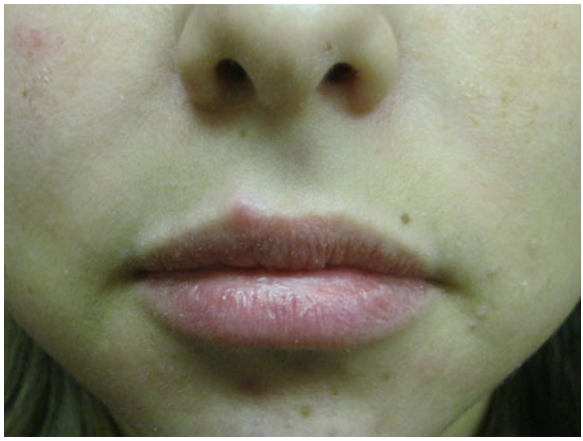

Fig. 13.1 Herpes labialis in early stage on the upper vermillion border

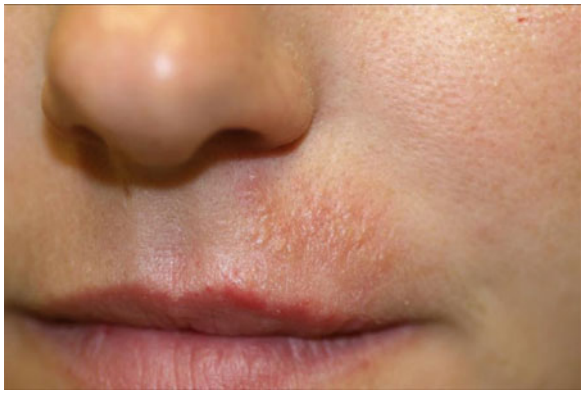

Fig. 13.2 Recurrent herpes labialis with nearby cutaneous involvement

periorbital edema and preauricular lymphadenopathy [1]. Corneal lesions with a branching dendritic pattern are pathognomonic [4]. Even with antiviral therapy, healing of the cornea can take up to a month [4, 6]. Approximately one-third of individuals experience a recurrence [1]; when they do occur, they are typically unilateral [4] and resolve over a period of weeks [4].

13.3.2.1 HSV in Immunocompromised Individuals

The degree of immune suppression correlates with the risk of developing HSV outbreaks. Organ transplant recipients and individuals with HIV/AIDS are at high risk for severe infections and frequent recurrences [4, 20]. The most frequent complication is progressive, chronic mucocutaneous infection with subsequent tissue necrosis [6]. Progressive disease involving the esophagus, respiratory, and gastrointestinal tract has been reported [4].

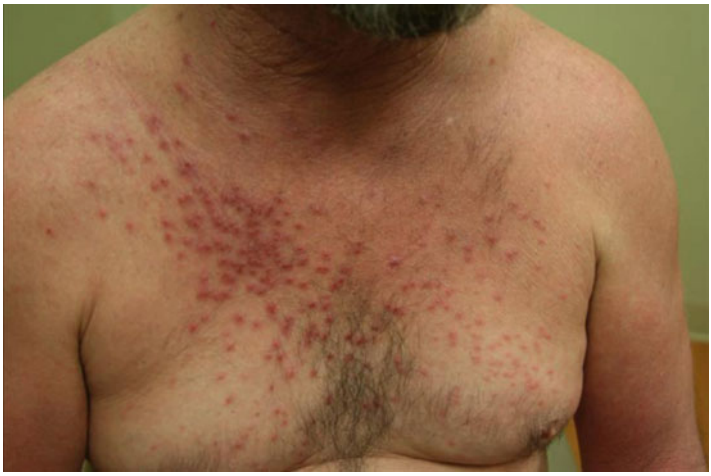

Fig. 13.3 Eczema herpeticum

13.3.2.2 Neonatal HSV

Neonatal HSV is defined as an HSV infection in a newborn within 28 days of birth. They are caused by viral exposure during vaginal delivery [21]. The risk of transmission is highest in mothers who acquire genital herpes near term [22].

There are three clinical presentations of neonatal HSV, each with a different prognosis. Because a rash is absent in 50 % of cases, all infants with CNS or sepsis symptoms should be evaluated for HSV. First, in 45 % of cases, infection is limited to the skin, eyes, and mucosa without CNS or visceral organ involvement. The vesicles that appear in these areas commonly recur in early childhood. Second, CNS involvement occurs in 30 % of cases; cutaneous signs are variable. Complications of CNS involvement include developmental delay, cognitive disabilities, blindness, and epilepsy. More than 50 % of children with HSV2 CNS infection have neurologic abnormalities. Finally, disseminated HSV occurs in 25 % of cases. It is indistinguishable from sepsis and has a 30 % mortality rate [21].

13.3.2.3 Miscellaneous HSV Infections

Individuals with a damaged epithelial barrier, most commonly from atopic dermatitis [23], are susceptible to eczema herpeticum. This presents as a vesiculopustular eruption in areas of underlying skin disease; lesions may erode and become secondarily infected. Recurrent episodes are generally less severe [24]. In wrestlers, herpes gladiatorum occurs in areas of close contact, usually the face and neck [25]. Facial HSV folliculitis presents as folliculocentric vesiculopapules and is confirmed histopathologically by HSV changes limited to the pilosebaceous unit [26] (Fig. 13.3).

13.4 Work-Up

Classically, detection is performed by viral culture in media that will show the HSV cytopathic effect, followed by typing with monoclonal antibodies [27, 28]. Viral swabs may be obtained from vesicles or other involved sites: oral mucosa, cerebrospinal fluid, or conjunctiva [4]. Polymerase chain reaction (PCR) has been the gold standard for diagnosing CNS infections and may become the standard test to diagnose HSV infections in other sites [29]. It has shown greater sensitivity than culture in detecting virus from oral [30] and genital lesions [31]. Serologic assays using enzyme-linked immunosorbent assay (ELISA) distinguish between HSV1 and HSV2 infections and detect infection in the absence of symptoms. Utilization of Western blot is restricted to research labs [4].

While not as sensitive as PCR [32], Tzanck smears allow for the cytopathologic detection of HSV. They are prepared by scraping the periphery of an ulcer, smearing the material on a glass slide, fixing immediately in cold ethanol, and then staining with Giemsa, Papanicolaou, or Wright stain [4]. Herpetic giant cells have multiple nuclei with molding and a ground-glass appearance, and intranuclear inclusion bodies [33]. Intranuclear inclusion bodies are not specific and may be seen in VZV infections as well [4]. Biopsy samples may show intraepidermal vesicles containing acantholytic keratinocytes with these cytologic changes [34] (Fig. 13.4).

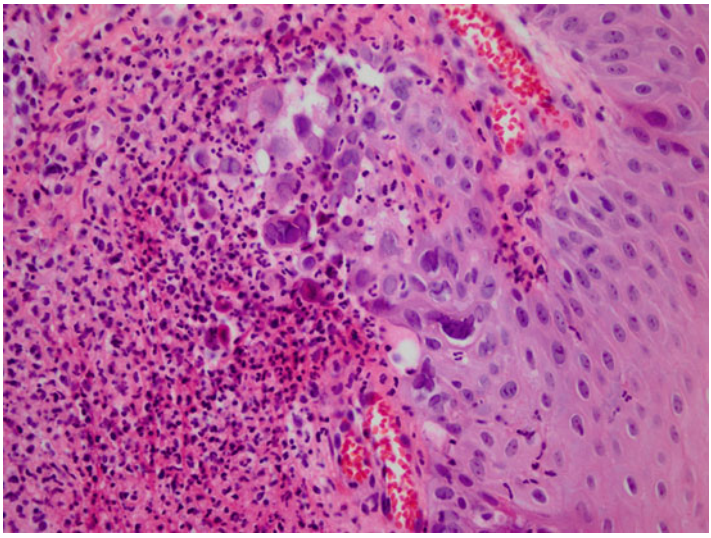

Fig. 13.4 HSV-infected cells with ground-glass nuclei, marginated peripheral chromatin, and a multinucleated giant cell with molding

13.5 Treatment

Most HSV infections are treated with acyclovir, its prodrug valacyclovir, and famciclovir (prodrug of penciclovir). These nucleoside analogues are activated by viral thymidine kinase and selectively inhibit viral DNA production by competing as substrate for DNA polymerase [6, 35].

13.5.1 Oropharyngeal and Orolabial HSV Infections

In moderate to severe primary disease in children, acyclovir 15 mg/kg five times per day for 7 days has been shown to decrease the duration of lesions from 10 to 4 days [11, 36]. Appropriate regimens for treatment of primary infections in adults include acyclovir 400 mg TID for 7–10 days, valacyclovir 1 g BID for 7–10 days, famciclovir 500 mg BID for 7 days, or 250 mg TID for 7–10 days [11, 37].

The ability to change the course of recurrent disease by administering antiviral therapy at the onset of symptoms has long been recognized [4, 15, 38]. Beginning treatment in this narrow therapeutic window is possible with patient-initiated episodic therapy, which reduces healing time to a greater extent than physician-initiated therapy [39]. First-line therapy in recurrent herpes labialis consists of famciclovir 1,500 mg once a day or valacyclovir 2 g twice daily for 1 day initiated at the first prodromal symptom [40, 41]. Suppressive treatment is not frequently practiced [40], but is effective at reducing recurrences [41, 42]. Valacyclovir 500 mg once daily is the simplest regimen [4].

Topical therapy includes docosanol 10 % cream (Abreva®) which demonstrated an 18-h reduced median time to healing in treated patients compared to placebo [43]. Penciclovir 1 % cream (Denavir®) and acyclovir 5 % cream (Zovirax®) both demonstrate therapeutic efficacy in early- and late-stage lesions [44].

13.5.2 HSV Keratoconjunctivitis

Trifluridine 1 % ophthalmic solution (Viroptic®) is the treatment of choice for primary and recurrent disease. Dosing is one drop every 2 h while awake (not to exceed nine drops per day). Once reepithelialization of the ulcer occurs, dosing continues at one drop every 4 h while awake for 7 days [4].

13.5.3 Mucocutaneous HSV in Immunocompromised Individuals

Acyclovir is effective in the prevention and treatment of HSV infections [4, 45]. For adults intravenous dosing is 5 mg/kg over 1 h, every 8 h for 7 days. In children, the

dose is 250 mg/m^2 with the same schedule. For limited disease, topical 5 % acyclovir ointment can be used every 3 h for 7 days [4]. One recent review found no evidence that valacyclovir is more efficacious than acyclovir [45]. In patients with HIV, episodic treatment with famciclovir 500 mg BID for 7 days or valacyclovir 500 mg to 1 g BID for 7 days is appropriate. The same regimen can be used off-label for chronic suppressive therapy [4].

Antiviral-resistant herpes virus, usually secondary to mutations in viral thymidine kinase, is a special concern in this population as suppressive therapy has become standard. In such cases, treatment with the pyrophosphate analogue foscarnet and the nucleotide analogue cidofovir are appropriate [46]. Standard drug-sensitivity tests take more than 10 days for a result, but newer, faster methods are being developed [47].

13.5.4 Neonatal HSV

Intravenous acyclovir 20 mg/kg every 8 h for 14 days is recommended for disease restricted to the skin and mucosa. The same regimen is extended to 21 days for disseminated and CNS disease. The 14-day regimen is considered appropriate therapy for asymptomatic infants born to mothers who acquired HSV infection near term [21].

13.5.5 Miscellaneous HSV Infections

Without controlled studies, it is intuitive that primary and recurrent cutaneous infections may be treated with valacyclovir or famciclovir at doses used to treat primary and recurrent herpes genitalis [4]. Prophylactic use of valacyclovir (500 mg or 1 g once or twice daily) is effective at preventing recurrences of herpes gladiatorum during the wrestling season [48].

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