Oral infections of herpes simplex virus: symptoms, diagnosis, treatment and pathophysiology in periodontal disease

Santhosh Basavarajappa[a], Ravikumar Ramakrishnaiah[a], Bangalore Durgesh[a], Abdulaziz A. Al Kheraif[a] and Darshan Devang Divakar[b]

There are many other viral agents that can affect the oral cavity in humans, either as localized or systemic infections; however, human herpesvirus is of clinical importance to the periodontologist. Although it exists in eight various forms, HSV-1 causes most of the oral infections. As dentists are more likely to be consulted in the case of oral infections, familiarity with these lesions becomes mandatory. Here, we have briefly reviewed the periodontopathic potential of the herpes simplex viruses: HSV-1 and HSV-2. Primary herpes infections typically occur during childhood or youth, although occasional cases are observed in older individuals. Recurrent HSV-1 infections typically occur throughout life and are particularly triggered by stress, illness, immune compromise, or other factors. It is more commonly reported in children and rarely in adults. Oral HSV infections' diagnosis and management are the primary responsibilities of the periodontal personnel. The current review discusses herpes simplex virus: oral infections' symptoms, diagnosis, treatment and pathophysiology of herpes simplex virus in periodontal disease.

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Introduction

The human mouth has a plentiful and multifaceted microbial population dwelling in various surfaces as a commensal microbiota. The oral microbiome includes *Streptococcus, Neisseria*, *Veillonella*, *Actinomyces* and other obligate anaerobes, in particular Bacteroides. Soon after birth, there is a rapid colonization with *Streptococcus salivarius, Streptococcus mutans and Streptococcus sanguinis*. Lack of oral hygiene, diet and certain other factors influencing the oral microbial community are responsible for subsequent oral diseases [1].

Among many thousands of oral and periodontal manifestations reported in the literature, only a few hundred are caused by viruses. Common among them are the group members of human herpesvirus and human papillomavirus families, which are of clinical importance to the periodontologist. As there is an increase in the number of iatrogenic immune-suppressed patients, there is a related increase in persistent viral and fungal infections. Perioral herpes simplex infections with oral lesions and mouth ulceration are particularly common [2].

Herpes simplex virus

Herpes simplex virus (HSV) is a double-stranded DNA virus belonging to human herpesviridae family. Eight types of herpes virus with distinct characteristics exist, of which HSV-1 causes different oral disease patterns. It is more commonly reported in children and rarely in adults.

[a]Dental Health Department, Dental Biomaterials Research Chair, College of Applied Medical Sciences, and [b]Dental Biomaterials Research Chair, King Saud University, Riyadh, Saudi Arabia.

Correspondence to Santosh Basavarajappa, Dental Health Department, College of Applied Medical Sciences, Dental Biomaterials Research Chair, King Saud University, P.O Box 10219, Riyadh 11433, Saudi Arabia.

Tel: +966 1 4696022; fax: +966 1 4693736; mobile: 966537137042; e-mail: dhd.ksu@gmail.com

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Human herpes simplex virions vary in size from 120 to 250 nm. HSV-2 causes genital herpes, but occasionally causes oral disease. HSV exhibits a short reproductive cycle with latency in the sensory ganglia. HSV causes a commonly known cold sore or a fever blister. HSVs are significantly associated with herpetic gingivostomatitis, recurrent orolabial lesions, herpetic whitlow, keratoconjunctivitis, eczema herpeticum, pharyngitis, mononucleosis-like syndrome, encephalitis, genital infections and Bell's palsy involving the cranial nerve. According to the data from the National Institutes of Health (NIH), United States, almost 90% of adults are exposed to the virus by the age of 50. Infected persons will carry HSV for the rest of their life; later, they may have primary or recurrent infections [3].

Although it exists in eight various forms, HSV-1 causes most of the oral infections. Since dentists are more likely to be consulted in the case of oral infections, familiarity with these lesions becomes mandatory. It is more commonly reported in children and rarely in adults [4].

Epidemiology and transmission

In immune-competent individuals, primary herpetic infections cause discomfort, but rarely cause significant morbidity or mortality. However, in immunosuppressed individuals, HSV primary infections are severe and may lead to oesophagitis, encephalitis, keratoconjunctivitis and sometimes death. Seroprevalence of HSV-1 varies between countries with some spectacular differences. The acquired ranges of age for HSV-1 infection is 5–9 years in central and eastern European countries where seroprevalence of HSV in Bulgaria is 83.9%, Czech Republic 80.6%, Belgium 67.4% and Finland 52.4%. In the Middle East, the prevalence of HSV-1 is comparatively high, with a high degree in Istanbul (99%), Israel (59.8%) and Eastern Anatolia Region (97%). However, the prevalence of HSV in Asian countries is relatively low: 51% in Thailand, 50–60% in Japan, 37% in East Asian countries and 9% in Philippines.

Primary herpes infections typically occur during childhood or youth, although occasional cases are observed in older individuals. Recurrent HSV-1 infections typically occur throughout life and are particularly triggered by stress, illness, immunocompromise, or other factors. Herpes zoster usually affects patients older than 40 years, and has similar triggers, although triggering conditions usually need to be more pronounced.

The common mode of transmission for HSV-1 and HSV-2 is contact with infected tissue; subclinical shedding may account for most of the transmission. HSV infection often spreads through skin contact, but it may also transmitted sexually including contact with saliva, such as kissing and oral sex [5,6].

However, HSV-2 is primarily a sexually transmitted infection, but recent reports suggest increased rates of HSV-1 genital infection [6]. Vertical transmission during childbirth is minimal if the mother has neither symptoms nor exposure to blisters during delivery; however, there is a risk when the mother encounters the virus for the first time during late pregnancy [7].

Genome structure

HSV types share a few common properties with other viruses of the family herpesviridae. Herpes virion consists of a double-stranded linear DNA genome encased in an icosahedral protein cage (capsid) wrapped in a lipid bilayer (envelope). HSV contain at least 74 genes [or open-reading frames (ORFs)] within their genomes, although speculation over gene crowding allows as many as 84 unique protein-coding genes by 94 putative ORFs. These genes encode a variety of proteins involved in forming the capsid, tegument and envelope of the virus, as well as controlling the replication and infectivity of the virus [8–10].

The genomes of HSV are complex and contain two unique regions called the long unique region and the short unique region. Of the 74 known ORFs, long unique region contains 56 viral genes, whereas short unique region contains only 12. Transcription of HSV genes is catalyzed by a RNA polymerase II of the infected host. Early genes are first expressed to encode and regulate the late viral genes, followed by the synthesis of enzymes involved in DNA replication and the production of envelope glycoproteins. The complete virion particle is formed by the expression of the late genes that encode proteins to form the icosahedral structure of HSV [9].

Symptoms and clinical features

HSV-1 has a predilection for the oral cavity, eye and skin causing orofacial infections, and HSV-2 has a predilection for the genital area and the newborn causing genital infections [11]. Herpes lesions occur around the lips, oral mucosa or tongue and last for a week to 10 days. The fluid-filled herpetic lesions may progress to shallow ulcers on gingiva, buccal and sublingual mucosa. HSV infections cause fever, anorexia, irritability, malaise and headache. In many cases, the lesions are subclinical and self-contained.

The most common clinical manifestation of HSV is herpetic gingivostomatitis, which is an infection of gums and mouth characterized by fever and submandibular lymphadenopathy typically affecting children and or adolescents who have not been previously exposed to the virus with frequent recrudescences wherein the virus

become latent in the host. Symptomatic primary herpetic gingivostomatitis, with multiple, small, clustered vesicles in numerous locations, can occur anywhere in the oral cavity, on the perioral skin, on the pharynx, or on the genitalia. Headache, fever, painful lymphadenopathy and malaise are common. Antibody production follows, and the virus may become latent in sensory ganglia, often the trigeminal ganglion. Primary herpetic gingivostomatitis usually resolves within approximately 14 days. Many primary infections are asymptomatic. Recurrent infections may occur extraorally or intraorally. Autoinoculation of the HSV virus to the distal phalanx of the fingers from the primary site of infection leads to herpetic whitlow.

Prodromal symptoms of primary HSV infections include severe, flu-like symptoms, swollen lymph nodes and headache. Some individuals experience no symptoms at all. Lesions in initial infections occur around the mouth and on oral mucosa and the tongue. People living in crowded and unsanitary conditions are more prone to HSV primary infections, which occur in almost every member of the population. Primary infection may become lethal in some cases of reduced immunity, concomitant eczema and the newborn [11].

The majority of recurrent herpes infection occurs as orofacial ulcers are widespread in immune compromised and renal transplant patients. These appear as clusters of painful small vesicles on the hard palate, gingiva and dorsal surface of the tongue, which rupture and ulcerate [3]. Recurring infections tend to be much milder, and the sores usually erupt at the edges of the lips. Some individuals never have any more symptoms beyond the initial infection. Recurrent herpes occurs in approximately one-third of patients who have experienced primary herpetic gingivostomatitis. When the disease manifests extraorally, prodromal burning or itching often precedes vesicle formation. Recurrent herpes is a more limited disease than primary herpes. Unlike primary herpes, it occurs on keratinized mucosa (usually the lips, attached gingiva and/or the hard palate). Vesicles are present in one discrete area, typically the same site every time in any given patient. Such sites include the perioral skin, the hard palate or, occasionally, the gingiva or the dorsal aspect of the tongue. One case report describes HSV-1 infection manifesting as a mass in the piriform sinus [12]. Because vesicles can easily rupture intraorally, only an ulcer may be observed in some cases. Lymphadenopathy and systemic manifestations are much milder than in the primary disease.

Similarly, lesions are found on the vermillion border of the lips, a feature of recurrent herpes labialis or fever blister, but lesions are also found on the mouth, face and inside nasal mucosa. Multiple blisters occur associated with severe discomfort that last for 10–14 days. Herpes recrudescences are triggered by exposure to sunlight, fever, physical or emotional stress, menstruation, UV radiation or systemic illness. Radiation-induced oral mucositis is caused by HSV group.

Ayangco *et al.* described erythema multiforme as a complex disease of skin and the mucosa developed as a secondary infection of HSV. Erythema multiforme is an acute mucocutaneous disorder, characterized by varying degrees of blistering and ulceration. A 20-year-old woman presenting with herpes labialis and with painful oral ulcers was diagnosed with erythema multiforme and treated illustrating the association of erythema multiforme with HSV infection [13].

The progression of recurrent oral HSV infection develops as follows:

(1) Initial redness, swelling, heat and pain, or itching in the area where the infection will erupt.
(2) Painful, fluid-filled blisters may appear on the lips or under the nose. These blisters, and the fluid they contain, are highly contagious.
(3) The blisters leak fluid and become sores.
(4) After approximately 4–6 days, the sores start to crust over and heal.

In immunocompromised individuals, recurrent herpes lesions may occur on any oral mucosal surface, including nonkeratinized sites. They also may manifest solely as lesions on the dorsal aspect of the tongue. Such a presentation has been variously reported as red or white nodules, painful nonvesicular ulcerations, fissured and, rarely, as a tongue mass [7]. Herpes lesions in immunocompromised individuals are often severe.

HSV-2 is also known as HSV-2, or genital herpes virus. HSV-2 infection is less common in the oral cavity than HSV-1 infection; however, its oral manifestations are clinically indistinguishable from HSV-1 infection [8]. Assessment of HSV-2 shedding by PCR has detected oral HSV-2 shedding in the absence of an oral lesion, but concurrent with genital HSV-2 reactivation. This was more common in HIV-positive males. In-vitro findings suggest that HSV-1 infection may induce the inflammatory response and affect periodontal health [14]. It may play a critical role in the pathogenesis of periodontal disease through the deregulation of the local cytokine network, resulting in an exacerbated response against a standard periodontopathogen infection [15].

Diagnosis

Diagnosis of some oral lesions is based on clinical appearance and behavior, whereas others require biopsy, culture or imaging for definitive diagnosis [16].

HSV is often confused with allergic reactions. HSV infections can only be confirmed with a virus culture, blood test or biopsy. A dentist diagnoses herpes infections by the position and appearance of the blisters. An oral sore in gingivostomatitis is diagnosed on their distinctive appearance and usually does not require more tests; biopsies and cultures are very rarely done. Rising antibody titers from initial and convalescent sera confirm primary herpetic gingivostomatitis. In herpetic labialis, fluids from the blisters are examined or cultured to confirm the diagnosis. Immunofluorescence is used in some cases to diagnose herpes infections [17]. Nitzan *et al.* compared cytological, virological and immunofluorescent methods to confirm the diagnosis of herpetic lesions and showed the reliability and applicability of fluorescent microscopy in the differential diagnosis of herpes infections [18,19].

There is no known association between recurrent intraoral herpes and more rapid progression of HIV disease. However, there is a clinical impression that recurrent herpes simplex infections may be more common in patients with symptomatic HIV disease [20]. HSV group is the predominant cause for AIDS-related oral ulcers/erosions of the epithelial layer on the palate, retromolar pad, tongue and lips [3].

Pathophysiology

The cytopathogenic effects, immune evasion and immunopathogeneicity and latency in the sensory ganglion constitute the main disease of HSV. Primary infection of HSV starts from entry of the virus, which then penetrates the mucosal epithelium and invades the cell of the basal layer, where the viral DNA inserts into the host DNA [5,6]. Viral replication occurs within the oral epithelium and lyses the epithelial cells, with vesicle formation. Shallow ulcers with scabs that heal without scarring follow the formation of vesicles. Herpesviruses can establish latent permanent infections in their hosts, although clinical signs of disease may not be detected.

Latent HSV infection may originate in the oral cavity because it is the preferential site for HSV antigens to hide. A study by Hochman *et al.* [21] demonstrated 60% patients with clinically healthy gingiva and patients undergoing periodontal treatment harbored herpes antigens in the sulcular epithelium and proved that stress and trauma can elicit herpetic recrudescence. Another study reported the prevalence of HSV-1 in chronic periodonditis by multiplex PCR and the rate of infection varied according to age and race of the population studied [22]. A prospective study by Amir *et al.* [23] described the clinical signs and symptoms, and complications of HSV-1 infections in young children. Herpetic gingivostomatitis is the severe manifestation of primary HSV and common in children leading to dehydration and sometimes secondary bacteremia. HSV was also demonstrated in few cases of acute necrotizing gingivitis [24]. Herpetic whitlow, an occupational hazard for pediatricians and other medical personnel, is a potential risk factor for the patients. Hence, early detection and prompt treatment are mandatory to limit the spread of infection [25]. Huang *et al.* studied the effect of HSV-1 on five different types of cell lines and described the characteristics of HSV-1-infected cells. It was shown that upon infection by HSV-1 virus there was an early phase of apoptosis and a late phase of necrosis followed by slow cell death in all the cell lines used. Since HSV-1 infection of both oral and nonoral cells was proved, the safety of using HSV-1 as a vector for gene therapy was suggested to be reconsidered [26].

HSV infection enhances the release of inflammatory mediators LTB_4 and interleukin-8, thereby inducing an inflammatory response that affects periodontal health. Active HSV infection leads to release of proinflammatory cytokines and activation of the T-lymphocytes and osteoclasts. Upregulation in the expression of tissue destructive matrix metalloproteinases from gingival fibroblasts and periodontium inflammation occurs. Immunosuppression as in HSV infection causes the overgrowth of secondary periodontopathic bacteria wherein the production of antibacterial antibodies is adversely affected because of lymphocyte cytotoxicity and cytokine release [3].

Prevention of infection

As HSV is transmitted through direct, physical contact, such as kissing and sexual contact, the best method of prevention is to avoid physical contact with the HSV sores. However, according to the Center of Disease Control and Prevention, genital herpes can be contagious without causing any symptoms of the disease and therefore can go unrecognized.

Treatment of infection

Treatment of viral gingivostomatitis mainly includes pain relief and prevention of dehydration. Normally, the blister or sores disappear in 1–2 weeks without treatment, but if the patient has frequent and persistent infection, antiviral medications can be prescribed, and the main antiviral drug used is acyclovir. Treatment success depends on the severity of symptoms. Specific treatment for HSV infection will be determined by age, health, medical history, extent of the disease and tolerance to medication. Otherwise, mouth washes, salt gargles or pain-killing cream may provide relief. The infected area should be kept clean and dry; topical antibacterial and

antiviral treatment and oral antiviral drugs help in recovering from the infection.

HSV-1-associated erythema multiforme major can also be managed with acyclovir prophylactically for 7 months [27]. The prophylactic effect of acyclovir was shown in patients with oral ulcers in acute myeloid leukemia receiving remission induction chemotherapy [28].

No treatment will permanently eradicate oral herpes simplex infections, but acyclovir may shorten the healing time for individual episodes. The optimum oral dosage of acyclovir is 1000–1600 mg daily for 7–10 days. Topical acyclovir is not useful for treating intraoral lesions and may not be effective for lesions on the lips.

Recurrent outbreaks of acyclovir-resistant herpes have been reported; in this case, the lesions resolved after treatment with foscarnet [29]. Phosphonoformate may also prove effective. Valacyclovir 1 g daily or placebo for 60 days can reduce the symptoms of the infection and also reduce viral shredding [5].

Conclusion

We have briefly reviewed the periodontopathic potential of HSV-1 and HSV-2 as well as the diagnosis and management of oral infections. This is the responsibility of the periodontal personnel.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the materials discussed in the article.

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