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Human herpesviruses: Research, and threats to health professionals

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Most practitioners are aware of the various effects of human herpesviruses on the body. Photographs of the most common dental and mucosal lesions are an integral part of their basic education. Among medical or dental patients, incidence of these conditions is high enough to keep practitioners versed in their recognition. However, research over the past several years has clouded the definition between previously independent diseases. For instance, oral and genital herpes simplex infections are no longer separate. Simple infectious mononucleosis is no longer just a matter of heterophilic antibodies, Epstein-Barr virus (EBV), or cytomegalovirus (CMV). A new herpesvirus, human herpesvirus-6 (HHV-6), has been shown to cause diseases, and has been implicated in other herpetic infections. To date, six types of human herpesviruses have been identified: herpes simplex virus 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), CMV, EBV, and HHV-6. Human herpesvirus-7, discovered in 1990, is not associated with a known disease.

With all herpesviruses, primary infection is followed by a latent period. HSV-1, HSV-2, and VZV lie dormant in the sensory ganglion. EBV remains latent in the B-lymphocytes and salivary glands. Some white blood cells appear to be the site for latent CMV; the nidus of HHV-6 probably is the lymphocytes. The exact mechanism of reactivation is still the subject of speculation, although answers are getting closer. Amstey, among others, notes that a common denominator for reactivation appears to be psychological or physical stress. It has long been known empirically that dental treatment or oral manipulation can cause reactivation of oral HSV disease. Within days following dental extractions, orolabial outbreaks develop in 10 to 15 percent of HSV-seropositive, asymptomatic patients. Recently, it was shown that selected viral genes actively produce certain cell-surface proteins during latent periods, a time in which they previously were believed to be totally quiescent. This might explain why 50 to 75 percent of genital HSV infections are acquired from asymptomatic sexual partners. A greater proportion of asymptomatic EBV infections probably are transmitted in a similar manner.

According to Wechsler, a molecular virologist involved with HSV research in California, a family of latency-associated transcripts (LATs) from a single gene in HSV-1 may play a role in reactivating the dormant virus. This LAT-producing gene is in a transcriptionally active region of the latent virus, and produces the only viral RNA detected during latency. It has been demonstrated that the promoter for this gene is neuron-specific, i.e., it turns on the gene only in neuronal tissue. Promoters are in a section of viral DNA just outside of their corresponding genes, and activate and deactivate the transcription of the gene. This contrasts sharply with the other 79 HSV-1 genes that are turned off in neuronal tissues. The LATs are presumed to play a role in the establishment, maintenance, or reactivation of latency. Wechsler reports that current speculation involves cellular stress or heat-shock proteins that are produced by body cells in response to stressful stimuli. Their production is increased by many of the same factors that lead to HSV-1 reactivation. The mechanism by which they might influence one another is unknown.

Clinical manifestations may accompany primary and recurrent herpetic infections. However, viral shedding during reactivation is common in all cases; viral particles commonly are found in the saliva. A unique characteristic of HHV-6 appears to be virtually constant shedding in the saliva. In cases of the other forms of herpes, shedding occurs at intervals. The effects of contact with saliva that is contaminated with the different types of herpesviruses are outlined below, and have been summarized elsewhere; infection-control measures are more critical when the mode or timing of the transmission of reactivated viruses is uncertain.

It is important for dentists to know that antibodies alone do not necessarily protect them from re-infection. In immunocompromised individuals, severe disease can result from reactivation by or re-infection with VZV, CMV, EBV, and HSV, and recurrent disease is common with VZV and HSV.

VZHV

VZHV usually causes chickenpox during primary exposure. The maculopapules (occurring centrally, spreading peripherally) proceed to vesicles and then scabs. Often, the first lesions occur intraorally (Fig. 1), VZHV is highly contagious through direct contact and airborne secretions. Viral transmission may begin several days before the skin erupts and continue until all of the lesions are crusted. Contact with saliva or respiratory secretions from a contagious source by a seronegative individual routinely results in viral transmission and subsequent development of chickenpox.

Reactivation leads to herpes zoster (shingles) in about 10 percent of the general population (mostly older persons). The factors that lead to VZHV reactivation are not understood. Reactivation is characterized by acute neuritis with
vesicular dermal or mucosal lesions in the dermatomes innervated by the infected dorsal root ganglia, usually thoracic or lumbar. Cutaneous manifestations of herpes zoster are not common but can involve any of the three branches of the trigeminal nerve. Herpes zoster ophthalmicus is associated with a high risk of mortality if cerebral angiitis is involved. Maxillary- and mandibular-branch involvement produces lesions in the pharyngeal walls, palate, tongue, and floor of the mouth. More severe cases are characterized by pain and vesicles in the external acoustic meatus, unilateral facial palsy, and loss of taste in the anterior two-thirds of the tongue. Fothergill neuralgia affects more than half of these patients who are older than 50.

CMV
During primary CMV infection, clinical disease may result. The immunological condition of the individual often determines whether the disease is manifest; healthy immunocompetent persons usually will not demonstrate clinical signs. CMV is responsible for infectious mononucleosis, pneumonitis, choriotitis, gastrointestinal disease, and meningoencephalitis. Reactivation and viral shedding of CMV rarely leads to clinical disease except in debilitated or immunocompromised patients. Seroconversion in childhood usually is through contact with others who are shedding virus in saliva or urine. Seroconversion later in life may occur through sexual contact with an individual who is shedding virus. When good personal hygiene and infection-control procedures are followed, there is little risk that health care workers will become infected.

It is now believed that the latent virus may remain in T-lymphocytes and monocytes. Serologic tests in cases of the most common form of CMV mononucleosis should indicate increasing antibody titer or, if antibodies are absent, seroconversion from negative to positive. Laboratory results that are not consistent with these usual findings may indicate a different causative virus than CMV (refer to the following discussions about EBV and HHV-6).

EBV
Primary exposure to EBV may not result in symptomatic disease. If infection occurs, the result is infectious mononucleosis. In infected children, the manifestations usually are mild; only half of infected young adults show signs of infection. Although viral shedding in the upper respiratory passages may persist for years following primary infection, most individuals recover fully. Virus is detected routinely in the saliva for months after acute infection, and intermittently throughout life. This long-term shedding is the source of transmission of the disease. Seronegative and immunocompromised individuals are especially at risk for contracting the disease from contaminated saliva.

Substantial antibody titers to EB antigens have been shown to persist for up to four years in many healthy individuals following acute infection. True chronic EBV mononucleosis is rare, and results directly from EBV infection. The condition is accurately diagnosed with serologic tests that show extremely abnormal EBV-specific findings. However, symptoms of chronic-fatigue syndrome (chronic mononucleosis syndrome), together with elevated EBV antibodies, are no longer believed to be caused by EBV mononucleosis. Straus et al. found that clinical symptoms of chronic-fatigue syndrome were not correlated with EBV antibody titer levels. The etiology of this syndrome is still unclear. Strong evidence shows that EBV may account for a number of lymphomas and nasopharyngeal carcinoma. EBV also has been implicated in cases of oral hairy leukoplaikia among homosexuals with AIDS. Infections from reactivation of the latent virus are more apt to recur in immunosuppressed individuals.

HHV-6
HHV-6 is the latest type to be identified and independently confirmed. Through the initial efforts of Salahuddin et al., and those of later researchers, the former human B-lymphotrophic virus, a lymphocyte-associated virus, was renamed HHV-6. The human immunodeficiency virus (HIV) (AIDS virus) specifically infects T-lymphocytes, which are critical in assisting the immune response, by attaching to a protein (CD-4 receptor) on the
cell surface. Interestingly, HHV-6 also infects and attaches to CD-4 receptors (on B-lymphocytes) in vitro.37 However, HHV is not as deadly as HIV, and only causes the common roseola infantum (exanthema subitum) in children. Why the similar CD-4 receptor on different cells does not attract both viruses is not known.

When recovered from saliva samples, HHV-6 affected more than 80 percent of the general population; 80 to 100 percent of adults under age 40, and 35 percent of persons who were 62.0 to 88.9 years old were seropositive. In a study of nine submandibular glands and four parotid glands submitted for routine biopsies on benign tumors or stones, HHV-6 was found in all of the submandibular glands and in one of the parotid glands. It is believed that seroconversion occurs early; in one study, more than 90 percent of children who were one to four years old were reported to be anti-HHV-6-positive.

This viral infection also has been linked to hepatitis and infectious mononucleosislike illnesses, besides roseola infantum.40-41 Buchwald et al. found chronic-fatigue syndrome in a previously healthy 17-year-old woman.42 The patient developed a mononucleosislike syndrome with chronic lymphadenopathy and splenomegaly. The severe symptoms lasted three years; hematologic and antibody tests were not consistent with acute infectious mononucleosis (EBV). A splenectomy was performed. After five years, the patient is better but remains chronically ill. Evidence of active replication of HHV-6 was found in the patient’s lymphocytes. However, antibody titers to other viruses elevate during chronic-fatigue syndrome, which clouds the significance of these findings.43 Cases of other mononucleosislike disease have been ascribed to primary HHV-6 infections.44-45

The highest HHV-6 antibody titers have been found in patients with EBV and CMV infections (another link to hepatitis and mononucleosis).46 Whether HHV-6 causes reactivation of other herpesviruses, or whether EBV-induced polyclonal B cell activation causes generalized viral antibody production remains unclear.47 Additional interaction between HHV-6 and HIV—both cause T4-lymphocyte depletion and ultimately death in HIV patients—has been speculated.48

HSV This group includes HSV-1 and HSV-2. Primary infections generally result in dermal and mucous-membrane lesions that are localized orally (Fig. 2), in the genitals, or in the ocular tissues. Owing to the contagious nature of the lesions from the time the vesicles rupture to the appearance of encrusted ulcers, self-infection is a strong possibility. Strict hygiene measures must be observed to prevent the spread from one body region to another. The virus may spread to the sensory ganglia that innervate the site of the affected region; HSV may spread to the central nervous system.1 HSV-1 is the most common cause of viral encephalitis in the United States (10 to 20 percent of all cases); if the condition is untreated, the fatality rate can approach 80 percent.49 In comparison, HSV meningitis, an acute disease associated more often with genital HSV infections, causes relatively few fatalities.

HSV infection has been associated with incidences of other diseases. Acute HSV infection and attacks of erythema multiforme appear to be connected. An attack of herpes simplex precedes up to 75 percent of cases of erythema multiforme.51 Correlations between HSV and cervical cancer have not shown a similar association. Likewise, no conclusive findings have resulted regarding an association between HSV and neurological disorders, hypothesized because of the affinity of the virus to attack nerve tissues. Certain cases of facial numbness have been associated with concomitant postherpetic reurrences. Gomina et al. reported cases of three patients with varied trigeminal neuropathy that resulted within one day of the development of a herpes simplex lip lesion. In conjunction with recurrence of the herpes simplex labialis, some aspects of these cases were: facial numbness involving the tongue and taste; paresthesia and tingling of the lower lip; paresthesia of the upper lip progressing to the entire V2 facial region; and transient, unilateral, acute-onset, trigeminal-sensory disturbance with a decrease in all sensory modalities except for corneal reflex and trigeminal motor activity.52

The older designations of oral (HSV-1) lesions and genital (HSV-2) lesions are invalid. Both types have genotypes that are approximately 50 percent homologous; neither type can be differentiated by clinical manifestations alone. If necessary, immunologic or genetic analysis is necessary for proper typing. Serological techniques must be used to detect antigenic differences between HSV-1 and HSV-2. Immunoperoxidation, immunofluorescence, enzyme-linked immunoadsorption, and microneutralization can be used. More than 50 percent of the world population (up to 100 percent of certain populations) has levels of antibodies to HSV-1; concentrations of antibodies to HSV-2 generally are lower but in a wider range of the population (5 to 95 percent). Seropositivity can correlate with age and low socioeconomic status.53

Exposure to and primary infection with HSV may not produce clinical lesions. Almost 90 percent of primary oral HSV infections are asymptomatic. However, the virus may be shed in saliva, without lesions present. Unconscious transmission is common given that an estimated five to eight percent of children and two to nine percent of adults may shed HSV asymptptomatically.54 After exposure, the signs usually appear in 1 to 26 days (incubation period). Tiny vesicles appear that rapidly ulcerate, crust, and heal (Fig. 3). Complete healing may take two weeks. The latent virus within the trigeminal ganglion may reactivate and cause herpes labialis (commonly called fever blisters or cold sores), perioral
lesions, or intraoral herpes simplex recurrence infection. Lesions recur in only one-third of persons with oral HSV.

Ocular infections generally result from self-infection from an oral outbreak. Such ocular infections—including blepharitis, conjunctivitis, keratitis, or chorioretinitis—usually occur unilaterally. Fifty percent of patients with ocular infections have an additional recurrence within one year, and may have scarring, and lose visual acuity—conditions that intensify with each recurrence. HSV infection is the leading transmissible cause of blindness in the United States.

Dermal infection is not common in areas other than tissues surrounding mucous membranes. Herpetic whitlow is gaining notoriety among health care providers as HSV infection is transmitted to the finger through contact with an active lesion. Dental personnel were especially susceptible before the institution of current aseptic barrier procedures.

Physically weak individuals with immunodeficiency and immunosuppression and persons with disorders of skin integrity have a high risk of contracting HSV infections. Transplant recipients and immunocompromised persons cannot effectively limit dissemination of the virus; consequently, rampant, fulminating HSV infections in such persons involve tissues that usually are not at risk. In AIDS patients, virus spreads along mucous membranes from external sites of infection, e.g., internally into the pharynx, esophagus, or bronchi, or into anal or colonic tissues. Similarly, burn victims or patients with dermatologic disorders (e.g., eczema or pemphigus) cannot confine the virus to primary sites of infection.

**Summary**

Increased awareness by dentists and the public about the risk of infection during treatment has spurred development of procedures that ultimately will protect everyone in the dental office. Constant discoveries are showing how vulnerable dental personnel are during dental procedures. The prevalence of potentially contagious and previously unknown viral entities in saliva, dermal and mucosal lesions, and respiratory secretions should not be underestimated. More than ever, barrier protection is essential. In a further effort to reduce exposure to practitioners, refusal to treat nonemergency cases during a patient's contagious periods should be considered.

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