

## VIRUS AND ORAL LESIONS

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### ABSTRACT

The oral cavity is particularly susceptible to viral infections because of its conformation, particularly its soft tissue and salivary glands. Several viruses, including herpes simplex virus (HSV) and human papillomavirus (HPV), are associated with oral disease-causing primary lesions. Prions are smaller than viruses and can only be seen through an electron microscope when they have aggregated and formed a cluster. Prions are also unique in that they do not contain nucleic acid, unlike bacteria, fungi, viruses, and other pathogens. The aim of this systematic review is to understand the association between viruses and oral lesions and about prions.

**Key Words:** virus, oral lesions, prions, HPV, HSV.

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## VIRUS AND ORAL LESIONS:

The oral cavity is a connection channel between outside environments and the respiratory tract and digestive tract. It provides an appropriate temperature, humidity, and nutrition for microorganism colonisation. The disturbance of the oral microbiota– ecology balance in the host usually causes a series of oral infectious diseases including dental caries, apical periodontitis, periodontal diseases, pericoronitis, and craniofacial bone osteomyelitis. Oral microbiota is also associated with several systemic diseases, namely cardiovascular disease, pneumonia, heart disease, rheumatoid arthritis, pancreatic cancer, colorectal cancer, oesophageal cancer, stroke, and adverse pregnancy outcomes.

## HOST DEFENSE AGAINST VIRUS:

The oral cavity possesses a series of physicochemical, cellular, and immunoglobulin barriers that prevent the entrance of harmful substances and microorganisms. However, physicochemical barriers within the oral mucosa, including saliva and oral epithelium, are not absolute. The saliva secreted by the major and minor salivary glands contains many non-specifically protective agents, such as mucin, lysozyme, lactoperoxidase, and lactoferrin. In particular, lactoferrin, an iron-binding glycoprotein of the transferrin family, can inactivate many deoxyribonucleic acid (DNA) and ribonucleic acid,” (RNA) viruses, including cytomegalovirus, HSV, and rotavirus <sup>(1)</sup>. Cellular barriers involve the cells of the gingival sulcus, inter-epithelial lymphocytes, and Langerhans cells. In particular, Langerhans cells, which are dendritic inter-epithelial cells and act as mucosa “sentinels are localized in the mouth inverse to the degree of oral mucosa keratinization and are primarily implicated in immune reactions. Despite these defense mechanisms, the oral mucosa is particularly subjected to viral infections

A virus is a sub-microscopic entity formed by a protein shell (known as a capsid) surrounding a single nucleic acid, DNA or RNA, only able to replicate in bacterial, animal, and vegetal cells. Viral genetic material is distinguishable from human genetic material due to its unique chemical and/or physical features. Also, a lipid envelope derived from the host cell membrane can be identified in some viruses. Even though viral infection can involve any human cell, the oral cavity offers an ideal entry into a new host. Some of the most well-known viral agents associated with oral lesions are HSVs and HPVs <sup>(2)</sup>. HSVs contain a double-stranded linear DNA molecule enveloped by an icosahedral capsid and a lipid casing. Initially involved in primary infections, they then remain dormant but can later cause secondary or recurrent infections. Eight types of HSV have been identified as human pathogens, and most are responsible for oral diseases. HPVs

are non-enveloped viruses containing double-stranded DNA. Over 100 subtypes of HPV have been identified, with at least 13 correlated to an insurgence of oral lesions. Members of the human herpesvirus (HHV) and human papillomavirus (HPV) families cause the most common primary viral infections of the oral cavity.

## HHV:

HHV infections are common in the oral cavity. They may be primary or recurrent infections. Eight types of HHV have been linked with oral disease <sup>(2,3)</sup>. These types have different disease patterns in their hosts.

1. HHV-1, also known as herpes simplex virus (HSV)–1, causes primary herpetic gingivostomatitis, or oral herpes. In some hosts, it becomes latent and may periodically recur as a common cold sore
2. HHV-2, also known as HSV-2, causes genital herpes and occasionally causes oral disease that is clinically similar to that of HHV-1 infection.
3. HHV-3, also known as varicella-zoster virus (VZV), causes the primary infection chickenpox and the secondary reactivation disease herpes zoster.
4. HHV-4, also known as Epstein-Barr virus (EBV), causes the primary infection - infectious mononucleosis, and it is implicated in various diseases, such as African Burkitt lymphoma, other immunoproliferative disorders, and nasopharyngeal carcinoma. HHV-4 causes oral hairy leukoplakia in patients who are immunosuppressed.
5. HHV-5, also known as cytomegalovirus (CMV), causes a primary infection of the salivary glands and other tissues, and it is believed to have a chronic form.
6. HHV-6, which can produce acute infection in CD4<sup>+</sup> T lymphocytes, causes roseola infantum, a febrile illness that affects young children. It is believed to chronically persist in salivary gland tissue in some hosts, and oral shedding is the probable route of disease transmission. Although it has been linked to apical periodontitis in some studies, the evidence so far is mixed, so such an association remains currently unproved.
7. HHV-7 has been isolated from the saliva of healthy adults and has been implicated as one cause of roseola infantum and febrile seizures in children.
8. HHV-8 is associated with Kaposi sarcoma (KS), and evidence links it with body-cavity lymphomas and Castleman disease.

Herpesvirus family members are icosahedral DNA viruses. A herpesvirus measures approximately 100 nm without an envelope or 150 nm with an envelope. HHVs replicate in the host cell nucleus. Infected saliva or droplets

spread the viruses in the oral cavity. The viruses also may be transmitted via oral-genital contact. Viral shedding has been detected before, during, and after the appearance of clinical lesions in patients with recurrent HHV-1 and HHV-2 infections; therefore, lack of visible lesions does not correlate with lack of potential infectivity<sup>(2,3)</sup>. In a localized primary infection, the virus penetrates the mucosal epithelium and invades the cells of the basal layer, where the viral DNA inserts into the host DNA. In HHV-1 and HHV-2 oral infections, viral replication within the oral epithelium may cause lysis of epithelial cells, with vesicle formation. Shallow ulcers with scabs that then heal without scarring follow the formation of vesicles. Herpesviruses establish latent permanent infections in their hosts, although clinical signs of disease may not be detected.

### **Clinical history for HHV-1**

Primary herpes infection (primary herpetic gingivostomatitis) usually occurs in children or adolescents who have not been previously exposed to the virus. Many primary infections are asymptomatic. Symptomatic primary infection, 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.

Recurrent herpes lesions are commonly referred to as cold sores. Recurrent herpes occurs in approximately one third of patients who have experienced primary herpetic gingivostomatitis. When the disease manifests extra orally, 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 vermilion border of the lips, the perioral skin, the hard palate, or, occasionally, the gingiva or the dorsal aspect of the tongue.

### **Clinical history for HHV-2**

HHV-2 is also known as herpes simplex virus type 2, or genital herpes virus. HHV-2 infection is less common in the oral cavity than HHV-1 infection; however, its oral manifestations are clinically indistinguishable from HHV-1 infection. Assessment of HSV-2 shedding by polymerase chain reaction 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

### **Clinical history for HHV-3**

HHV-3 is also known as varicella-zoster virus. HHV-3 is responsible for chickenpox and shingles.

Primary varicella, or chickenpox, usually occurs in children aged 3-6 years who are not immunized at the time of their first exposure to the virus. Itchy vesicles begin on the skin of the trunk and spread to the skin of the head. Intraoral and pharyngeal vesicles may occur. Antibody production follows, and the virus usually becomes latent in the dorsal root ganglia.

Recurrent varicella, also known as herpes zoster or shingles, usually occurs in adults, and its incidence increases with age. It can occur in any patient who has had chickenpox and only rarely occurs in patients who have received chickenpox immunization. Recurrent varicella may occur when cellular immunity decreases. It results in a vesicular rash that usually affects a single dermatome. Inside the oral cavity, this may be observed as vesicles or ulcerations that stop sharply at the midline. A prodrome of pain, burning, or itching that mimics a toothache may occur.

Ramsay-Hunt syndrome arises when the virus emerges from latency in the geniculate ganglion. It involves cranial nerve VII (facial nerve), which has both motor and sensory functions.

Manifestations may include paralysis that involves the levator palati muscle and the face; hoarseness; loss of secretory function (eg, dry mouth, loss of taste); vertigo; tinnitus; pain; and vesicles involving the pharynx, the eardrum, the external ear, or the tympanic membrane. Persistent facial nerve weakness or deafness may follow.

### **Clinical history for HHV-4**

HHV-4 is also known as Epstein-Barr virus. HHV-4 is most commonly known as the agent that causes infectious mononucleosis. Primary infection, infectious mononucleosis (colloquially referred to as “mono” or “kissing disease”), occurs on first exposure to the virus, usually during young adulthood. It is often a subclinical infection. The virus (usually acquired from infected saliva) replicates in the cells of the mucosa and salivary glands and spreads to B lymphocytes and the bloodstream. If the patient is immunocompetent, cytotoxic T cells become activated and a characteristic lymphadenopathy (notably involving the posterior cervical nodes) accompanies tonsillitis and hepatosplenomegaly.

Hairy leukoplakia, caused by HHV-4, primarily occurs in adults who are immunosuppressed. Hairy leukoplakia

manifests as asymptomatic white lesions on the lateral border of the tongue, often bilaterally. The lesions have a corrugated, linear appearance and may appear granular or nodular or may have hairlike projections.

#### **Clinical history for HHV-5**

HHV-5 is also known as cytomegalovirus. Primary HHV-5 infection is usually asymptomatic in patients who are immunocompetent. The virus is shed by glandular secretions, including saliva. It occasionally is shed in urine. Primary HHV-5 infection can be asymptomatic, but it can also mimic mononucleosis. Clinical disease is more common in neonates and in patients who are immunosuppressed than in other individuals

#### **Clinical history for HHV-7**

HHV-7 infection has been associated with roseola infantum, acute hemiplegia of childhood, respiratory tract infections, and hepatitis. It has also been linked to seizures in children with febrile illnesses. HHV-7 has been identified in the saliva of adults, and this is most likely where the virus persists chronically.

#### **Clinical history for HHV-8**

HHV-8 is also known as KS-associated herpesvirus, because DNA sequences of HHV-8 have been identified in persons with Kaposi sarcoma (KS), and, therefore, it is believed to be important in causing and/or maintaining KS lesions. KS in the oral cavity follows the same disease pattern as KS in other body sites<sup>(2,3,4)</sup>. Initially, the lesion may appear as a red, purple, or dusky patch that enlarges into a plaque and later progresses into a tumorous mass.

#### **HPV:**

HPVs are members of the Papovaviridae family, which are small icosahedral viruses that contain circular DNA.

HPV is a 50-nm virus composed of double-stranded DNA with no envelope. The virus penetrates the mucosal epithelium and invades the cells of the basal layer, where the viral circular DNA inserts into the host DNA.

Verruca vulgaris, or common warts (HPV-2; HPV-4; occasionally HPV-1, HPV-3, HPV-27, HPV-29, and HPV-57), are more common on the skin than in the oral cavity. On the oral mucosa, the warts are usually sessile, verrucous, and white; solitary or multiple; and elevated with discrete borders. The lesions most commonly occur on the lips, hard palate, or gingiva. Verruca plana is similar but less elevated. Warts are commonly observed on the digits of patients with oral infection.

Condyloma acuminata, or genital warts (usually HPV-6, HPV-11; occasionally HPV-30, 40, 42, 43, 44, 45, 51, 52, 54, 61, 70, 72, and 81), may affect the oral mucosa as well as the genitals, perianal region, larynx, or trachea. These lesions are usually cerebriform, pink, and sessile and solitary or multiple; they occur more commonly on nonkeratinized mucosa than on keratinized mucosa.

Focal epithelial hyperplasia, or Heck disease (HPV-13, HPV-32), typically manifests as multiple, smooth, sessile nodules, often on the mucosal surface of the lower lip or on the buccal mucosa.

#### **PRIONS:**

The term “prions” refers to abnormal, pathogenic agents that are transmissible and are able to induce abnormal folding of specific normal cellular proteins called prion proteins that are found most abundantly in the brain<sup>(5)</sup>.

Prions as infectious, transmissible proteinaceous particles that lack nucleic acid. The normal cellular prion protein (PrP<sup>c</sup>) is encoded by PrP<sup>c</sup> gene, which is located on the short arm of chromosome 20. PrP<sup>c</sup> has predominantly alpha helical structure, is soluble and proteinase sensitive. The normal function of PrP<sup>c</sup> is not well-known, but the suggested functions are signal transduction, cell adhesion, regulation and distribution of acetylcholine receptors.

PrP<sup>c</sup> is transformed into abnormal isoform of the protein (PrP<sup>Sc</sup>) due to post translational modification or mutation in the PrP<sup>c</sup> gene. PrP<sup>Sc</sup> has predominantly beta structure, is insoluble and partially proteinase resistant. This mutated PrP<sup>Sc</sup> gives rise to TSEs, including bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and goats and Creutzfeldt-Jakob disease (CJD) in humans<sup>(5,6)</sup>. These diseases are characterized by vacuolization of the gray matter and these vacuoles are located in the neuropils between the nerve cell bodies.

The abnormal folding of the prion proteins leads to brain damage and the characteristic signs and symptoms of the disease. Prion diseases are usually rapidly progressive and always fatal.

Prion diseases or transmissible spongiform encephalopathies (TSEs) are a family of rare progressive neurodegenerative disorders that affect both humans and animals. They are distinguished by long incubation periods, characteristic spongiform changes associated with neuronal loss, and a failure to induce inflammatory response.

The biosynthetic pathway followed by PrP<sup>c</sup> is similar to that of other membrane and secreted proteins, involving synthesis on ER-attached ribosomes, transit to the Golgi, followed by

delivery to the cell surface. PrP<sup>C</sup> is a glycoprotein, with two N-linked oligosaccharide chains of the complex type.

Several intriguing lines of evidence have emerged recently suggesting that PrP<sup>C</sup> may exert a cytoprotective activity, particularly against internal or environmental stresses that initiate an apoptotic program.

PrP<sup>C</sup> itself acts directly to detoxify reactive oxygen species (ROS).

PrP<sup>C</sup> acts indirectly to protect cells from oxidative stress by up-regulating the activities of other proteins, such as Cu-Zn SOD, that detoxify ROS.

PrP<sup>C</sup> possesses a biological activity that is lost upon conversion to or contact with PrP<sup>Sc</sup>. Loss of this putative PrP<sup>C</sup> function would then cause neurodegeneration. In principle, loss of any of several of the putative functions of PrP<sup>C</sup> discussed above could produce pathogenic consequences. However, the anti-apoptotic activity of PrP<sup>C</sup> is most easily accommodated in such a mechanism, since loss of this activity could lead directly to neuronal death<sup>(5,6)</sup>.

PrP<sup>Sc</sup> has been detected by polyclonal antibodies to scrapie associated fibril/prion protein in the trigeminal ganglion of one patient with fCJD and one patient with sCJD. These workers also noted the presence of specific immunostaining of dystrophic axons in the nerve roots and around the degenerating ganglion cells of the trigeminal ganglion, suggesting centripetal or centrifugal extension of the disease process along the axons. Positive immunochemistry for PrP has been reported for the trigeminal ganglion in vCJD but was not detected in cranial nerves or salivary gland tissue. One study has investigated the levels of prion protein in pulpal tissue from eight patients with sCJD. By Western blotting, using a specific monoclonal antibody, this group was unable to detect any prion protein in pulpal tissue. However, the authors suggested that since the method used was relatively insensitive, the potential for transmission of CJD via dental procedures, although low, could not be dismissed. These workers calculated that 1 g of sCJD infected pulp would be expected to contain 40 log<sub>10</sub> LD<sub>50</sub>/g of infectivity, compared with 10<sup>8-9</sup> LD<sub>50</sub>/g of infectivity in brain tissue.

## CONCLUSION:

Viruses rely on a host cell for growth and replication. As a consequence, it is often difficult to stop viral replication without damaging the host. Prions are infectious proteins that cause neurodegenerative diseases in mammals. The amyloid state that is typical of the aggregated pathogenic form of the prion protein is also found in proteins involved in other neurodegenerative diseases.

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