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World Journal of Stomatology

Contents

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MINIREVIEWS

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World Journal of Stomatology (*World J Stomatol*, *WJS*, online ISSN 2218-6263, DOI: 10.5321) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJS covers topics concerning oral and craniofacial sciences, oral and craniofacial development/growth, dental tissue regeneration, craniofacial bone and cartilage research, oral and maxillofacial genetic diseases, developmental abnormalities and soft tissue defects, pulpal and periapical diseases, periodontal diseases and oral mucosal diseases, salivary gland diseases, oral and maxillofacial vascular/nervous diseases, jaw bone diseases, taste abnormalities, oral and maxillofacial pain, occlusion and temporomandibular diseases, repair and treatment of tooth defects, loss and dento-maxillofacial deformities, oral and maxillofacial biomechanics and biomaterials, new techniques for diagnosis/treatment of oral and maxillofacial diseases; and stomatology-related evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of stomatologic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJS*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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Impact of different types of herpesviral infections in the oral cavity

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Abstract

The herpesviruses are ubiquitous, doubled-stranded DNA viruses that can reactivate under conditions such as immunosuppressive therapy, acquired immunodeficiency syndrome, malnutrition, and immunosenescence. There are eight types of herpesviruses: Human herpesvirus simplex (HSV) type I (HSV-1) and HSV type II (HSV-2), varicella-zoster virus (VZV), epstein-Barr virus (EBV), cytomegalovirus, human herpesvirus (HHV)-6, HHV-7, and HHV-8 or Kaposi's sarcoma herpesvirus. Some of these viruses can infect the oral cavity, leading to different types of lesions. Specifically, labial herpes (HSV-1 and less frequently HSV-2), zoster (VZV), infectious mononucleosis and oral hairy leukoplakia (EBV), and Kaposi's Sarcoma (HHV-8) are the most common viruses infecting the oral cavity. Some of these viruses can act in synergy with other herpesviruses or as distinct infectious agents. Other herpesviruses may have indirect effects in periodontal disease. The diagnosis is frequently based on signs and symptoms and depends on the experience of the examiner. Cytopathologic and/or histopathologic examination as well as immunological methods such as ELISA could help to elucidate cases. In addition, molecular techniques which can be sensitive and specific have been reported in the literature. These methods require low amounts of sample and could offer results faster than other traditional methods.

Key words: Herpesvirus; Oral cavity; Symptoms; Infection; Virus

Core tip: The oral lesions caused by herpesviruses can be painful and not always easily diagnosed and treated. This review article intends to briefly describe the viral features, physiopathology, epidemiology, signs, symptoms, laboratory diagnosis and its limitation, and typical therapy and prevention (if it exists) of these oral lesions. The main aim of this present article is to help the clinical practice considering diagnosis of the oral herpesviral infections. In addition, there is a lack of an

updated article concerning basic and clinical information about herpesvirus infections.

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INTRODUCTION

Human herpesviruses belong to the *Herpesviridae* family, and they are ubiquitous. After the primary infection, the individual remains latently infected during the individual's lifetime. These viruses cause a wide variety of diseases, often benign, however, in immunocompromised individuals, they can cause clinical symptoms of varying severity[1].

The *Herpesviridae* family is divided into three sub-families: Alphaherpesvirinae (α-herpesvirinae), Betaherpesvirinae (β-herpesvirinae), and Gammaherpesvirinae (γ-herpesvirinae). All of these viruses are double-stranded DNA viruses and share similar structural features. There are eight different types of herpesviruses which infect humans, and some of them can also infect animals. Table 1 displays a list of viruses belonging to the herpes group that infect humans[1,2].

The viruses of the herpes group establish primary infections with few symptoms, which may result in efficient immune response to prevent a reinfection. However, the virus is not eliminated completely, and its genome is maintained in certain cells without a productive infection. Latent infections can become active (reactivation) due to host factors, and these events allow the spread of the virus[2,3].

Human herpesvirus simplex (HSV) type Ⅰ (HSV-1) and HSV type Ⅱ (HSV-2) are usually associated with labial and genital herpes, respectively. However, genital herpes may be a consequence of infection by HSV-1, and labial herpes can also be caused by HSV-2[4]. Varicella-zoster virus (VZV) causes varicella (chickenpox) in primary infection that occur especially in children, and the reactivation can cause the onset of zoster herpes, which occurs more frequent in the elderly[5,6]. Epstein-Barr virus (EBV) is associated with infectious mononucleosis, Burkitt's lymphoma, and nasopharyngeal carcinoma[7,8]. Human herpesvirus (HHV)-8 or Kaposi's sarcoma herpesvirus (KSHV) is associated with Kaposi's sarcoma and can lead to death in immunocompromised patients, particularly in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients[9]. A primary cytomegalovirus (CMV) infection causes a syndrome similar to mononucleosis known as "cytomegalic inclusion body disease"[1]. Primary infections of HHV-6 and HHV-7 cause a common infectious febrile syndrome in infancy known as exanthema subitum or roseola[10,11].

The labial lesion caused by HSV is the prototype of herpesviral infection, and it is the most well-known among the clinical manifestations to lay individuals. However, genital infections and other clinical manifestations caused by the other listed above herpesviruses are less well known.

HSV

Labial herpes and stomatitis

The most cases of labial herpes are caused by HSV-1, whereas HSV-2 usually infects the genital area. However, cases of HSV-1 in the genital area have been reported[12-14]. The primary HSV infection could occur in early childhood by direct contact with lesions of an infected individual or *via* domestic utensils contaminated with biological fluids derived from lesions or saliva[12,15]. The main symptoms of labial herpes are painful bullous lesions occasionally accompanied by fever[4]. Normally, the infections self-limited and disappears four or five days after onset of symptoms. However, in some individuals, the lesions could have more severe outcomes affecting extensive labial areas and internal parts of the mouth referred to as stomatitis or gingivostomatitis, occasionally presenting esophagitis[16-18]. Immunosuppressive states such as chemotherapy, immunosupresive therapy in autoimmune diseases, or transplantation[19], malnutrition, and AIDS manifestation increase the risk of disease[1,20].

After the contact with viable viral particles, the virus infects and replicates in epithelial cells and local nerves, causing lesion and pain[21]. Furthermore, cellular immune responses try to eliminate infected cells followed by neutralization of extracellular viral particles, leading to disappearance of viral replication and symptoms. Residual pain and signs of lesion cicatrix may linger, despite clearing of viral replication.

The contact with individuals who present lesions increases the rate of viral transmission, but HSV could theoretically be transmitted by contact with non-symptomatic persons. Occasionally, viral particles are shed in saliva of healthy individuals, therefore transmission of the virus by this pathway may be possible[15]. It is important to note that viral load is crucial for transmission and direct contact with symptomatic individuals (*e.g.*, kisses) or sharing of cups, dishes, and forks should be avoided.

After primary infection, the virus can remain latent during its lifetime and can be reactivated intermittently, or nevermore to cause symptoms. The virus can be latently harbored in peripheral neurons or "at a low" level of replication well controlled by the immune system. Under immunosuppressive conditions, the virus can escape immune vigilance *via* evasion mechanisms, causing new lesions, frequently with the same topography of the past infection[4,15,21]. However,

Table 1 Complete list of the human herpesviruses

Virus	Synonymous	Subfamily	Abbreviation
Human herpesvirus-1	Herpes simplex-1	α	HSV-1/ HHV-1
Human herpesvirus-2	Herpes simplex-2	α	HSV-2/ HHV-2
Human herpesvirus-3	Varicella-zoster	α	VZV/HHV-3
Human herpesvirus-4	Epstein-Barr	γ	EBV/HSV-4
Human herpesvirus-5	Cytomegalovirus	β	CMV/HHV-5
Human herpesvirus-6	None	β	HHV-6
Human herpesvirus-7	None	β	HHV-7
Human herpesvirus-8	None	γ	KSHV/ HHV-8

HSV-1: Herpes simplex virus type 1; HSV-2: Herpes simplex virus type 2; VZV: Varicella-zoster virus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; KSHV: Kaposis's sarcoma-associated virus; HHV: Human herpesvirus.

severe immunosuppression does not seem to be strictly necessary to herpesviral reactivation. For instance, labial lesions caused by recurrent HSV may occur in immunocompetent individuals after exposure to cold, sunlight, lip injury, and stress[4]. To note, 60%-90% of the adult population has an IgG positive serostatus for HSV, but not all experience HSV reactivation.

The diagnosis of labial herpes and stomatitis is based on signs and symptoms, but it is important to ensure differential diagnosis of other oral manifestations such as aphthosis and stomatitis caused by *Candida albicans*. The laboratory diagnosis is frequently not necessary, but it can be made by detection of IgM antibodies against the virus, smears of lesions stained by Giemsa[16], biopsy, or by molecular methods[17].

The use of IgM detection is limited specially by two different conditions. In the reactivation state, the infection may not produce IgM antibodies to detectable levels, leading to a false negative result. In addition, the level of IgM antibodies from a previous episode of infection can remain high (residual IgM), causing a false positive result. The determination of specific IgG avidity may help to elucidate and better guide diagnosis because high IgG avidity suggests recent HSV infection.

The histological sections of tissue obtained by biopsy or smears of secretions collected by deep scrape from lesions can be stained by Hematoxylin-eosin (HE), Giemsa, or Papanicolaou[16]. The cytopathic effects are relatively easy to be identified by an experienced pathologist. However, the cytopathic effects cannot be distinguished from the effects of other herpesviruses (*e.g.*, VZV). Immunohistochemistry/immunocytochemistry using specific anti-HSV mAbs can be employed to discern between other herpesviruses. Naturally, due to an invasive feature of biopsies procedures and pain caused by lesions, the actual importance of these procedures in each case must be carefully evaluated.

The molecular methods are the most conclusive tests, although they are more expensive. Polymerase chain reaction (PCR) is a sensitive and specific molecular method used to detect viral agents, and the results can be obtained in a few hours. There are different PCR methods which can vary in several technical and economical aspects. Typically, DNA is extracted from swabs of lesions, and viral DNA is amplified by the use of specific primers followed by qualitative or quantitative detection of specific products (amplicons). It is important to note that the primers must be able to amplify either HSV-1 and HSV-2[17].

The therapy for labial herpes is regularly not necessary, but the use topic acyclovir[22] can accelerate recuperation. In association with an adequate analgesic drug, this is a good therapeutic strategy. Extensive labial lesions or stomatitis can be treated with oral or injectable acyclovir. Preventive anti-HSV treatment with oral acyclovir has been used for solid organs and bone marrow transplantations[23].

VZV

Varicella and zoster

VZV primary infection occurs mainly in childhood, and it is called varicella or "chickenpox", which affects the skin and mucosa. The illness appears as a bullous lesion in the overhaul of the body, and it often affects the internal mouth and lips[1,24]. Among the symptoms included are itch, pain in the lesion area, and fever. Chickenpox is typically benign and requires only symptomatic treatment, but in some cases, it can lead to severe disease such as hepatitis or encephalitis.

In the oral mucosa, secondary infection can occur and treatment with antibiotics or with antifungal drugs must be considered in these cases. VZV, like HSV, remains latent in the peripheral nerves, and it can reactivate in immunosuppressive states, being classified as "zoster"[25]. Indeed, the zoster is the reactivation of latent VZV virus acquired by a past varicella episode. Zoster differs from varicella due to the fact that it only generally infects locally along nerve. The most common affected areas are dorsal, lateral parts of the chest, the legs, and the face. Also, zoster can infect the lips[26]. When the virus infects the lips, the lesions are clinically indistinguishable from HSV lesions[26].

Zoster causes discomfort, reduces physical, emotional, and social functioning, induces lower vitality, and impairs physical and mental health. Zoster-causing lesions are frequently accompanied by neuralgia[27]. AIDS and therapy with immunosuppressive drugs are the main causes of zoster, however, malnutrition and aging are also strongly associated with zoster. Indeed, the frequency of zoster in the elderly is relatively higher compared to younger people[28]. The vaccine for varicella is available but has mainly been used in epidemic cases and outbreaks. It is rarely included in routine vaccinations. Recently, the use of vaccination in the elderly for prevention of zoster has been proposed[27,29,30]. However, the efficacy has not been completely established, and it seems to prevent neuralgia but not zoster *per se*[29]. Obviously, the

prevention of neuralgia helps to minimize the severity of disease and enhances the welfare of the elderly. Unfortunately, the vaccination is not yet economically affordable to a great part of the population.

The laboratory diagnosis of VZV is relatively easy by use of immunological methods for detection of IgM against VZV. However, the immunological diagnosis of zoster is not easily achievable due to the same conditions described above for HSV infections. The biopsy or smears of secretions (Tzanck smear) help to elucidate and discern VZV infections[31], but the cytopathic effects are indistinguishable of HSV lesions unless mABs against VZV are used in immunohistochemistry/immunocytochemistry procedures. Furthermore, PCR using specific primers for VZV can make the diagnoses definitive[32].

EBV

The most known and common syndrome of EBV infection is mononucleosis. Many teenagers and young adults develop symptoms of mononucleosis. Acute mononucleosis causes sore throat, fever, and swollen lymph nodes. Sore throat is very painful and is the usual reason for people to seek medical attention. The tonsils may become very swollen. In addition, loss of appetite, fatigue, chills, headache, bloating, sore muscles, body aches, weakness, and sweats are commonly described and experienced. Most of the symptoms disappear completely in days to a few weeks, however, signs of fatigue could remain for a few additional weeks[7,33].

Some patients can have neurological complications such as encephalitis, meningitis, or inflammation of an individual nerve[34]. The majority of patients with neurological complications recover completely. However, some patients can develop EBV-induced lympho-proliferative disorders which may be either related to immunocompetent or immunosuppressed patients[35,36].

EBV has been related to some forms of neoplasia, such as Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, and conditions associated with HIV such as oral hairy leukoplakia, and lymphoma of the central nervous system[37,38]. EBV is also associated with oral hairy leukoplakia which consist of a white plaque on the lateral part of the tongue that cannot be removed by gentle scraping[39]. It is most common in people with HIV/AIDS as aforementioned or other immunosuppressive states, such as organ transplantation.

Other types of tumor are associated with EBV, however, the mechanism which EBV contributes the transformation of normal lymphocytes in tumor cells is not completely known.

HHV-8/KSHV

HHV-8 is the least prevalent among all human herpesviruses. Asymptomatic infection can occur, but the most known manifestation of this infection is Kaposi's Sarcoma (KS)[40].

KS is a neoplasia of the endothelial cells, and it presents as four epidemiological types: Classic, endemic, post-transplantation, and associated with AIDS. The tumors mainly affect the skin, but it can cause lesions in internal organs and the mouth. Especially in AIDS patients, the oral manifestations can appear as a pustular lesion. Screening for HIV is a standard procedure when KSHV-induced oral lesions are found in the patient. The oral lesions can affect the tongue, lips, gums, tonsils, and the inner cheek. Biopsies with immunohistochemistry using mAbs against HHV-8 or PCR are the conclusive diagnostic methods[41,42].

KS tumors are treated with chemotherapy, radio-therapy, or immunotherapy, and the use of anti-HIV prophylactic drugs decreases the risk of developing KS.

ASSOCIATION BETWEEN HERPESVIRUSES WITH GINGIVITIS AND PERIODONTITIS

While gingivostomatitisis caused by HSV, the role of other herpesviruses in periodontal tissue remains to be elucidated. Some studies have suggested that the presence of herpesvirus in periodontal regions could play a role in the pathogenesis of human periodontitis[43-45]. As mentioned before, herpesviruses are ubiquitous and can persist latently after primary infection in various types of host cells, including cells of the immune system. CMV is the most studied member of the *Beta-herpesvirinae* sub-family in the periodontal regions. Recently, other herpesvirus (EBV, HHV-6, and HHV-7) have been investigated with regards to periodontitis since these viruses are often found in the saliva[43-45]. Herpesviruses have also been studied in other diseases, and some studies have suggested that these viruses may act directly or indirectly by immunomodulation, specifically by influencing the immune responses due to viral replication in lymphocytes and monocytes/macrophages.

Inflammatory cells harboring herpesvirus present in periodontal inflammation sites may contribute to the development and progression of periodontitis[46-48]. CMV can induce direct cytopathic effects on fibroblasts, keratinocytes, endothelial cells and inflammatory cells, polymorphonuclear cells, T-lymphocytes, macrophages, and possibly bone cells. In patients with periodontitis, T-cells are activated, and specific lymphocyte responses are moved by the nature of the original antigenic stimulus. This process is supported by a complex cascade of events involving cytokines, chemokines, and other inflammatory mediators that can be changed due to CMV infection. Balance between pro-inflammatory and anti-inflammatory activities controlled by different sub-populations of lymphocytes seem to be pivotal in the pathogenesis of periodontitis[49].

Local immunomodulatory effects caused by infection

with herpesviruses may facilitate bacterial growth and increase the virulence or inducing release of cytokines and chemokines from inflammatory cells and connective tissue. Furthermore, viruses and bacteria can act in synergy to produce pathology. Moreover, the presence of betaherpesviruses in regions affected by periodontitis could merely reflect latent virus in periodontal tissue or cell inflammatory infiltrate present in this kind of pathology[43,48].

Studies conducted in our center found that 30% of periodontitis patients have CMV and/or HHV-7 as detected by qualitative nested-PCR in the tissue[50]. CMV was associated with inflammatory infiltrates that presented higher amounts of T-cells, and HHV-7 infection presented with higher amount of $CD4^+$ T-cells. Based on those findings, two hypotheses were formulated: (1) The viruses may be active, and they may have direct or indirect effects on periodontitis; and (2) The viruses may be latent, and the presence of viral genomes merely indicates that cells harboring virus migrated to the affected area due to inflammation.

Posteriorly, we studied the viral replication by use of immunohistochemistry to detect viral antigen in gingival biopsies collected from periodontitis-affected areas. The study aimed to differentiate active or latent infection because detectable viral antigens appear only in active infections. Interesting, none of the samples presented viral antigens suggesting latent infection (unpublished data). The use of nested-PCR yielded is very sensitive results as this method can detect low amounts of viral DNA that typically is found in latent infections, thus being therefore able to indicate "true" infection in the samples.

CONCLUSION

Among the eight herpesviruses, HSV-1 (maybe HSV-2), VZV, EBV and HHV-8 can be directly linked to oral lesions. The conditions of the immune system significantly influence the risk of developing these infections. Additionally, immunosuppression, malnutrition, and immunosenescence are the most frequent disorders involved in the reactivation of herpesviruses. The differential diagnosis of other infections is very important to ensure the proper treatment of patients.

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