VIRUS AS A CAUSE OF SALIVARY GLAND DISEASES

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ABSTRACT

Background: Enlargement in the extraoral region with the absence of abnormal dental and periodontal structures are sometimes seen in dental practice, sometimes followed by xerostomia. Enlargement of the acute nonsuppurative salivary glands has been associated with several types of viruses. The purpose of this paper is to review salivary gland diseases associated with non-HIV and HIV viral infections.
Discussion: Non-HIV viruses which were detected in the salivary glands including Paramyxovirus, cytomegalovirus (CMV), Hepatitis C virus (HCV), human papilloma viruses (HPV), Epstein-Barr virus (EBV), human herpes simplex virus (HHSV-8), and coxsackie virus. HIV-associated salivary gland disease typically presents with xerostomia and/or intraglandular lymph nodes, and diffuse infiltrative lymphocytosis syndrome (DILS). The most common viral infection conditions in salivary gland disorders are mumps and HIV. Enlargement and inflammation of the glandular structures will affects the control of salivary secretion by nerves. Parasympathetic nerves block conducted signals to the salivary glands, so the salivary flow is decreased.
Conclusion: There is association between viral infection and diseases of the salivary gland. By knowing sequelae viruses on the salivary gland, dentists are expected to understand the clinical condition and therapeutic that should be given to the patients.

INTRODUCTION

Saliva is a complex combination of fluids, electrolytes, enzymes, and macromolecules that together do several important functions: lubrication to help swallowing; producing amylase enzymes to help digestion; taste modulation; protection against caries and pathogens.[1–3] The salivary glands are the paired parotid, submandibular and lingual glands along with several hundred minor salivary glands, distributed through the upper aerodigestive system.[1,4,5]

Salivary gland disorders are often associated with viral infections.[1,4,6–8] Enlargement of the acute nonsuppurative salivary glands has been associated with several types of viruses.[4,7] Viruses that cause most gland enlargement are paramyxovirus, cytomegalovirus (CMV), hepatitis C virus (HCV), Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV), Human Herpes Virus 8 (HHV-8) and HIV. [4,9–15] Other virus detected in Saliva are coxsackie virus, influenza, parainfluenza virus, echovirus, BK virus, Human T-lymphotropic virus (HTLV), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), Kaposi sarcoma virus (KSHV), guinea pig CMV, mouse CMV (MCMV), mouse polyomavirus (PyV), encephalomyocarditis (EMC).[6,9] Sometimes accompanied with xerostomia as the manifestation of viral infection.

HIV-associated salivary gland disease typically presents with xerostomia and/or swelling of the major salivary glands. It encompasses multitude of conditions like lymphoepithelial lesions, cysts involving the salivary gland tissue and/or intraglandular lymph nodes, Sjogren's syndrome-like conditions, diffuse infiltrative

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lymphocytis syndrome (DILS), and other reported lesions of the major salivary glands.[16–19] About 5% of HIV patients exhibit HIV-Associated salivary gland disease (HIV-SGD).[8]

In this literature study, we dividing viral infections salivary gland disease due to non-HIV and HIV. The purpose of this paper is to review salivary gland diseases associated with non-HIV and HIV viral infections.

LITERATURE REVIEW

Viruses in Latin means venom or poison. Viruses are ultramicroscopic organisms which breed in living cells, inert metabolically, capable of infecting other organisms. The size of viruses ranges from 10 millimeters or less to more than 200 millimicrons. The virus consists of a DNA or RNA nucleus, surrounded by a capsid made of protein or an outer envelope made of glycoproteins and lipids derived from the host cell membranes.[8,9,11,13,14]

Classification of diseases caused by viruses is difficult because of the virus size and metabolic system that have not been fully understood. International Committee on Nomenclature of Viruses of the International Association of Microbiological Societies has classified them into groups according to the type of nucleic acid, the size, shape, and substructure of the particle.[8]

Paramyxovirus, cytomegalovirus (CMV), hepatitis C virus (HCV), Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV), Human Herpes Virus 8 (HHV-8) and HIV are several viruses that causing salivary gland enlargement and sometimes xerostomia. [4,9–15] In this paper we will review those viruses, divided into non-HIV viral infections of the salivary gland and HIV associated salivary gland disease.

Non-HIV Viral Infection of The Salivary Gland

Paramyxovirus/Mumps

Mumps is an acute, self-limiting, contagious viral infection characterized chiefly by unilateral or bilateral swelling of the parotid, although all salivary glands may be involved.[8,9] 85% of cases occur in children younger than 15 years.[1,9] Human are the only natural host. Infection occurs following exposure through the upper respiratory tract by droplet, aerosol, direct contact, or fomites. The prodromal symptoms are fever, malaise, and headache. Approximately 24 hours later, glandular swelling, tenderness, and associated earache can occurs. Resolution of symptoms generally occur in 10 days.[9] Complications including orchitis, acute pancreatitis, meningoencephalitis, deafness, and mastoiditis.[8,9]

Mumps should be differentiated from other parotid swelling which were caused by influenza, parainfluenza 1 and 3, coxsackie, HIV, cytomegalovirus, Sjögren's syndrome, pleomorphic adenoma, etc.[8] Diagnosis is confirmed through viral serology test. The treatment are supportive measures, including hydration, rest, oral hygiene instruction and pain control or antipyretic.[4,9] According to Centers for Disease Control and Prevention (2014), vaccination is 88% effective in preventing mumps and has reduced the incidence by 99%.[1] Currently, the CDC recommends mumps patients should avoid contact with others from the time of diagnosis until at least five days after the onset of parotitis by staying at home from work or school and in a separate room if possible.[4,23]

Cytomegalovirus (CMV)

CMV (HHV-5) is a member of the Herpesviridae family. As the characteristic of other members of Herpesviridae, CMV can become latent after initial exposure and infection and

may become reactivated when favorable conditions are present. The majority of CMV infections are asymptomatic, especially in healthy individuals; however, in immunocompromised patients and neonates, the infection can be life-threatening. In the young adult, acute CMV infection presents with fever, malaise, myalgia; pharyngitis and lymphadenopathy. Oral and maxillofacial manifestations of CMV in immunosuppressed patients typically present as persistent oral ulcerations and major salivary gland infections, with or without concomitant alterations in salivary flow.[4,24] CMV infection has been investigated as one of the causative agents in Sjogren's syndrome with a molecular mimicry mechanism of pathogenesis. Viruses affect exocrine tissue primarily through plasmacytoid dendritic cells (pDCs) and Toll-like-receptors (TLRs).[25] Transmission occurs through blood transfusion, allograft transplants, sexual contact, fomites, urine, saliva, and respiratory secretions.[4,24,26] In HIV-positive patients, the degree of CMV-induced sialadenitis and/or xerostomia was found to be proportional to the viral load and inversely proportional to the CD4+ cell count.

Several diagnostic modalities for CMV are available including serology, qualitative and quantitative PCR, as well as histopathology. The choice of test is based on the status of the immune system of the patient. Treatment in those with symptomatic infection are supportive and symptomatic care (i.e., analgesics, rest, hydration). Immunocompromised patients require aggressive antiviral therapy that may be in the form of ganciclovir, valganciclovir, foscarnet, or cidofovir.[4,24]

Hepatitis C Virus (HCV)

Hepatitis C virus (HCV) is one of the major causes of chronic liver disease worldwide, as the global estimated prevalence of HCV is 2.2% with 40-75% of patients with chronic HCV infection exhibit at least one clinical extrahepatic manifestation (EHM).[15,20] HCV infection has many extrahepatic manifestations, including sialadenitis and chronic major salivary gland enlargement and complaints of xerostomia and sicca syndrome (Sjogren-like sialadenitis) are common.[4,20,27]

The diagnosis of HCV infection is established by the serologic detection of anti-HCV antibodies by ELISA and HCV DNA by PCR. Treatment of patients with acute HCV infection receives weekly PegIFN-alpha or standard interferon. Hepatitis-associated sialadenitis and xerostomia are treated symptomatically.[4]

Human Papilloma Virus (HPV)

Human Papilloma Virus (HPV) has been demonstrated to be the trigger of neoplastic diseases of the head and neck.[10,28] Moreover, the medical literature provides only little evidence about the role of HPV in salivary gland tumors.[13,29] HPV-16 and HPV-18 are the most commonly detected high-risk types.[28,30,31] Due to the growing rates of salivary gland tumors and positivity of HPV types 16 and 18, some studies hypothesized that use of the two available HPV vaccines for cervix carcinoma may cause a reduction of salivary gland cancer.[29–32]

Table 1. Differences between sialadenitis in Sjogren's syndrome and hepatitis C virus. Modified from Carrozzo M et al.[15]

Variable	**Sjogren's syndrome**	**Hepatitis C virus**
Sicca symptoms	Commonly present	Usually absent or modest
Parotid swelling	Moderate to severe	Mild to moderate
Extra glandular manifestation	Mainly pulmonary, gastrointestinal, renal, and neurology involvement	Mainly gastrointestinal and musculoskeletal involvement

Epstein-Barr Virus (EBV)

Same like HPV, studies in head and neck neoplasms revealed that Epstein-Barr virus (EBV) have implicated as aetiological factors.[11] EBV is an enveloped DNA herpesvirus that is transmitted by saliva and is shed even in apparently healthy subjects. EBV not only found in malignant neoplasms like salivary gland lymphoma, but also in benign lesions such as lymphoepithelial cyst and Warthin's tumor.[11,33] Some studies have been founded that EBV is the co-factor in the development of Sjogren's syndrome.[25]

Human Herpes Virus 8 (HHV-8)

Human Herpes Virus 8 (HHV-8), a gamma-2 herpes virus (rhadinovirus) which naturally infects only humans, is the cause of several neoplastic disorders among immunocompromised individuals, especially Kaposi's sarcoma, although salivary gland Kaposi's sarcoma is rare. Dalpa et al, 2007 investigate that HHV-8 infection could play a role in a subset of adenoid salivary neoplasms.[9,12]

Coxsackie Virus

Coxsackie virus is an RNA virus potential localized, presence and replicates in exocrine glands of patients with Sjogren's syndrome. Triantafyllopou et al, 2004, reported for the first time an association of a coxsackievirus infection with primary Sjogren's syndrome. Coxsackie virus replication takes place in the submucosal lymph tissue and then disseminates to the reticuloendothelial system. Further dissemination targeting the organs occurs following a second viremia. RNA from two strains, CVB4 and CVA13,has been identified in minor salivary gland samples from pSS, therefore implicating Coxsackie virus of a potential environmental trigger for Sjogren's syndrome.[25,34–36]

HIV-Associated Salivary Gland Disease (HIV-SGD)

HIV-SGD is define as AIDS in pediatric HIV infection and has increased in the adult HIV population.[6,16] Typically, HIV-SGD presents a unilateral or bilateral diffuse soft swelling resulting in facial disfigurement, and may be associated with pain.[6] As HIV progresses, salivary glands are infiltrated with CD8 lymphocytes leading to diffuse infiltrative lymphocytosis syndrome, resulting in salivary gland enlargement.

Another manifestation of HIV-associated salivary gland disease is that qualitative and quantitative xerostomia (reduced salivary secretion) may occur. The causes of xerostomia including drugs (antiretrovirals, antifungals, chemotherapeutics, antihistaminics, mood-altering drugs, multivitamins), oral diseases (candidiasis) or as a part of the progression of the HIV disease.[8,17] There are evidence that HIV-SGD increases with HAART therapy.[6] The dentist should identify xerostomia early and provide nutritional counseling as well as preventive treatment with fluorides and other agents including chlorhexidine/benzydamine hydrochloride and triclosan/fluoride mouth rinse.[18] Management of HIV associated xerostomia involving antiretroviral therapy, oral hygiene instruction, and sialagogues.[1]

Diffuse Infiltrative Lymphocytic Syndrome (DILS)

DILS is characterized by salivary and lacrimal glandular swelling and sicca symptoms of various degrees of intensity, accompanied by a proliferation of CD8+ lymphocytes and lymphocytic infiltration of the various organ including parotid glands, lacrimal glands, kidneys, muscles, nerves, lungs, and lymph nodes in association with HIV infection.[6,16] DILS mimicking Sjogren's syndrome in terms of sicca symptoms, salivary glandular enlargement, histology, and predisposition to develop non-Hodgkin's lymphoma.[6]

Table 2. Comparison of Salivary Gland Disorders: HIV-associated Salivary Gland Disease vs Sjogren's Syndrome[6]

HIV-SGD/DILS	SS
• An AIDS defining illness in pediatric HIV infection, affecting up to 60% of children worldwide	• The second most common autoimmune rheumatic disease, affecting 1to 2 million Americans, with women affected 9x more frequently than men
• Incidence is increasing in the adult HIV population and post HAART has become a hallmark of HIV associated immune reconstitution syndrome	• EBV, KSHV, Coxsackie and HIV have been investigated as potential etiologic agents
• Infiltration of CD 8+ T-cells	• Infiltration of CD4+ T-cells

DISCUSSION

The viral organism that first comes to mind when considering non-HIV viral infections of the salivary glands is the mumps virus. The mumps virus is a paramyxovirus from influenza and Newcastle groups. Like measles, it is a single-stranded RNA virus. Humans are the only natural host.[9] Some systemic complications may be serious, including meningitis, encephalitis, hepatitis, carditis, orchitis and hearing loss, therefore the patient must be isolated for several days.[4,7] Vaccine has been reported eradicated outbreaks.[9] The treatment are supportive care.

Several viruses, including DNA, RNA, and retroviruses have been considered as the important co-factors in the development of Sjogren's syndrome. The two DNA viruses that have been studied in association with Sjogren's syndrome are cytomegalovirus (CMV) and Epstein-Barr virus (EBV).[25,36,37] Overall the data regarding CMV and EBV as causative agents for Sjogren's syndrome are contradictory, and, because Sjogren's syndrome does not occur in most cases of viral infection in vivo. The link between reactivation and autoimmunity induction remains to be established. Epstein Barr virus (EBV), human papillomavirus (HPV), human herpesvirus-8 (HHV-8) have an association with tumorigenesis and lead into some neoplasm in salivary gland.[11–13,33] Two RNA viruses have been detected within the salivary glands of Sjogren's syndrome patients i.e. hepatitis C virus (HCV) and Coxsackie virus, both of which require more investigation before they are classified as being the etiological agent of Sjogren's syndrome.[20,25,34–36] The diagnosis can be confirmed by viral serology examination.

The epidemiology of HIV-SGD strongly suggests the involvement of a viral opportunist in its pathogenesis.[16] The conditions that associated with HIV including xerostomia, DILS, lymphoepithelial lesions of the parotid gland, CMV infection, hepatitis C virus infection, mumps, sialodenosis, parotid cysts.[4,8,16,17] Another significant increase in prevalence of HIV-SGD was reported in patients under highly active antiretroviral therapy (HAART) in the AIDS population.[19] The relationship between HAART and HIV-SGD may be due to the patients in early stages of the disease who remain in the initial phase of HAART therapy and still have relatively high viral loads and are thus subject to an increased risk of developing HIV-SGD.[16,19]

The most common viral infection conditions in salivary gland disorders are mumps or HIV with swelling as the clinical presentation, often bilateral; may be tender, followed by xerostomia. Xerostomia is defined as the subjective sensation of oral dryness that may or may not be associated with a reduction in salivary out-

put. Xerostomia may be transient, prolonged or permanent depending upon the duration of the condition. Acute viral infection is the temporary cause of xerostomia, meanwhile, Sjogren's syndrome and tumor that precipitated by viral infection, are the permanent cause.[37–39] Salivary gland cells are intimately associated with the autonomic nervous system. Parasympathetic and sympathetic nerves run together with Schwann cells to the target cells in salivary glands. Parasympathetic stimulates saliva, and sympathetic is inhibiting saliva production. Parasympathetic and sympathetic nerves are in contact with many types of cell in salivary glands, including acinar, ductal and myoepithelial cells as well as blood vessels.[40,41] Enlargement and inflammation of the glandular structures will affect the control of salivary secretion by nerves. Parasympathetic nerves block conducted signals to the salivary glands, therefore the salivary flow is decreased.

CONCLUSION

There is association between viral infection and diseases of the salivary gland. In general, viral infection of the salivary gland may result in swelling and/or reduced saliva production. By knowing sequelae viruses on the salivary gland, dentists are expected to understand the clinical and therapeutic conditions given to patients.

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