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Salivary gland disease in human immunodeficiency virus/ acquired immunodeficiency syndrome: A review

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Abstract

The effect of human immunodeficiency virus (HIV) infection on salivary glands has diagnostic and prognostic significance. HIV-salivary gland disease (HIV-SGD) is comprehensively ascertained amongst the major critical acquired immunodeficiency syndrome (AIDS)-related oral manifestation and causes substantial morbidity. Parotid gland swelling due to sicca syndrome, parotid lipomatosis, sialadenitis, diffuse infiltrative lymphocytosis syndrome, benign lymphoepithelial lesions, neoplasms (benign or malignant) of salivary gland, parotid gland inflammation, diminished flow rates of saliva and xerostomia have been documented that also affects the health- associated characteristics of life in subjects infected with HIV. There is a necessity for health care researchers to diagnose it, particularly as it might worsen if left undiagnosed. The precise characteristic of alterations in dynamics of salivary gland structure and functionality with long-standing usage of highly active anti-retroviral therapy still remains unknown. HIV positive children also present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of predominated lymphoid hyperplasia. Though various case reports and studies have been extensively published on different aspects of HIV-SGD, it has not been described solely, thus leading to occasional confusion of nomenclature and clinical presentation of HIV-SGD. This article reviews the pathogenesis of HIV-related SGD and its components and various other miscellaneous disorders affecting the salivary glands in HIV/AIDS.

Key words: Human immunodeficiency virus; Acquired immunodeficiency syndrome; Salivary gland diseases; Antiretroviral therapy; Highly active; Xerostomia

Core tip: Since the discovery of human immunodeficiency virus (HIV), the world has kept acquired immunodeficiency syndrome high on the agenda, rallying around global and regional commitments to turn the tide on HIV infection. There is limited data on the documentation of HIV salivary gland disease and the influence of highly active anti-retroviral therapy occurring on various components of salivary gland disorders in HIV. The purpose of

writing this article is to review the clinical manifestations and the pathogenesis of salivary gland disorders in HIV in era of antiretroviral therapy and provide an update on latest treatment modalities in the management of various salivary gland disorders.

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INTRODUCTION

Since the discovery of human immunodeficiency virus (HIV), the world has kept acquired immunodeficiency syndrome (AIDS) high on the agenda, rallying around global and regional commitments and goals to address and turn the tide on HIV infection. HIV affects almost all the structures in the body. Patients with HIV infection are prone to salivary gland disease. The initiation of highly active antiretroviral therapy (HAART) has coincided with reduced prevalence of oral manifestations in HIV/AIDS infected patients in the developed and developing countries. These oral manifestations can act as markers of immune reconstitution or as a marker of HAART failure. However, there is limited data on the documentation of HIV salivary gland disease (HIV-SGD) and the effect of HAART on various components of salivary gland disorders in HIV. In resource constrained nations, the relatively easier diagnosis of HIV-SGD can help in the early diagnosis of HAART failure, thus helping in an early initiation of other drugs in HAART. The purpose of writing this article is to review the clinical manifestations and the pathogenesis of salivary gland disorders in HIV in era of antiretroviral therapy and provide an update on the latest treatment modalities in the management of various salivary gland disorders.

HIV-SGD

The latest criteria given by the Oral HIV/AIDS Research Alliance (OHARA) gives description of SGD as asymptomatic long standing enlargement of parotid glands, usually bilaterally[1]. The clinical presentation of HIV-SGD simulates Sjögren's syndrome. There are however noticeable serologic and histopathological distinctions concerning both the diseases[2]. There is absence of anti-Ro (SS-A) and anti-La (SS-B) antibodies in subjects with HIV-SGD. HIV-SGD is typically seen in young males as compared to Sjogren's syndrome that occurs predominantly in middle aged females[2]. In HIVSGD, minor salivary gland histopathology constitutes predominantly periacinar, perivascular, and periductal lymphocytic infiltrates with most of the penetrating cells being CD8 cells[2]. With the advent of HAART, the prevalence of HIV-SGD has increased in developed countries. The prevalence has been reported to be 5% (Patton *et al*[3]) - 10% (Mandel *et al*[4]). Navazesh *et al*[5] had found an increased prevalence of HIV-SGD in a study of HIV infected women where HAART primarily comprised of Protease inhibitors. In contrast, in developing countries there have been few cases of HIV-SGD following HAART[6-8]. The probable association between HIVSGD pathogenesis and BK polyomavirus (BKPyV) has been validated with demonstration of HIVSGD-derived BKPyV oral tropism and proficient viral copying in salivary gland cells[9]. The presence of lymphoid tissue within a salivary gland capsule has been observed only in parotid gland while the submandibular lymph nodes lie adjacent to, but outside the glandular capsule[9]. An awareness of HIV-SGD may prevent unnecessary surgeries in these patients, a biopsy being necessary only in those cases suspected of harboring a malignancy[10]. The homeostasis of the oral cavity is altered in subjects with HIV-SGD due to quantitative variations ensuing in the saliva such as reduced secretory levels of lysozyme, sodium, calcium chloride, total anti-oxidant capacity and cystatin[11].

XEROSTOMIA AND HAART

HIV infected patients have been reported to be having a considerably greater possibility of salivary gland hypofunction and xerostomia as compared to patients who are not infected[12]. Xerostomia has been documented in HIV subjects with varying prevalence ranging from 10% in American homosexual males, 9% in 74 Dutch patients, 35.5% of 200 Indian patients, and 80% patients from Peru[13-16]. The reduced absolute CD4 cell counts were substantially correlated with a greater frequency of zero unstimulated salivary flow rates in HIV patients[17]. Lin *et al*[18] had reported that there is reduction in unstimulated salivary flow rates and stimulated salivary flow rates even in early stages of HIV infection. Reduced salivary flow rates have also been attributed to HIV infection, side effect of HAART, or in correlation to considerable salivary gland disease[19,20]. It is difficult to determine whether the subjective alterations related to salivary flow (hyposalivation, xerostomia, and dysgeusia) can be attributed to HIV disease or HAART[21]. Among HAART, protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTIs) have been especially been known to induce xerostomia probably by exertion of an anti-secretory effect on acinar cells[12]. Other researchers had suggested that the PIs changes adipose tissue deposition within the salivary gland[22]. However López-Verdín *et al*[21] and Nittayananta *et al*[6] found no significant difference in salivary flow rates when they compared HAART with PIs and HAART without PIs.

HIV p24 antigen in the salivary gland and a viral load of greater than 10000 copies were also found to correlate with a higher prevalence of xerostomia[23]. There was a reduction of stimulated and unstimulated salivary flow rates in HIV patients on HAART[6,12]. A considerable diminution of saliva in response to proportion of the increased number of years of usage of antiretroviral therapy has

also been reported[21]. However documentation in all the epidemiologic studies has relied on the presumptive criteria of EC-Clearinghouse classification which will not give the true prevalence of xerostomia. Most studies have been done on limited sample size, have been cross sectional and the terminologies of salivary gland hypofunction and xerostomia have been interchanged frequently for subjective signs and objective clinical observations[12]. The subjective (finding negligible saliva) and objective (*i.e.*, clinical presentation of major salivary glands, stimulated and unstimulated salivary flow rates) processes have been comprehensively documented in very few studies[6,12,17]. However, studies have taken different parameters like unstimulated and chewing gum stimulated whole saliva and parotid gland saliva. Wang *et al*[24] had found unstimulated whole salivary flow rates to be more sensitive to dry mouth complaints rather than stimulated whole salivary flow rate. Therefore research should be conducted on unstimulated whole saliva in a preferably longitudinal study to understand the exact effects of HAART and HIV on salivary gland hypofunction.

The sequelae of reduced salivary flow are increased caries prevalence, increased oral candidiasis, dysguesia and periodontal diseases[17,21]. The Usage of crystal methamphetamine is frequented with greater HIV acquisition, and it is correlated to sudden generalized dental caries recognized as "meth mouth" in HIV positive patients[25]. Lithium, muriatic and sulfuric acids and lye, the constituents of crystal methamphetamine, have been considered as causative factors. In a study conducted in 2009, high concentrations of the HIV p24 antigen in the salivary gland and a viral load of greater than 10000 copies were found to correlate with a higher prevalence of xerostomia[5].

PAROTID LIPOMATOSIS

Abnormal fat deposition in HIV patients on HAART (PI) has been documented in abdomen, dorsal cervical areas and Parotid gland[26]. Olivé *et al*[27] were first to document parotid lipomatosis in two patients on Protease Inhibitors. The protease inhibitors stimulate peripheral lipodystrophy that is triggered by inhibition of proteins which control metabolism of lipids[26]. The above process ensues in decreased differentiation and a rise in peripheral adipocytes's apoptosis with impaired fat storage[27].

LYMPHOEPITHELIAL CYSTS

A rare condition of Lymphoepithelial lesions observed in the parotid gland is correlated with a greater frequency in HIV patients[28]. The persistent generalized lymphadenopathy (PGL) is a characteristic feature of HIV patients. Lymphoepithelial lesions represent a probable confined or limited expression of PGL[28]. However, the etiopathogenesis of lymphoepithelial lesions is still unknown. The lymphoepithelial lesions may originate from inclusions of the major salivary gland located in lymph nodes (mainly intra-parotid lymph nodes). Another possibility of lymphoepithelial lesion developing from the parenchymal component of the salivary glands has also been postulated[28-30]. Parotid lympho epithelial cysts are easily diagnosed by ultrasonography. These lesions often become large leading to societal stigmata[28]. The lymphoepithelial lesions are typically benign. However there is always a distinct possibility of their conversion to lymphomas. Thus, continuous and periodic follow-up should be conducted for these lesions and should not be disregarded[31]. There are also bilateral parotid swellings observed in diffuse infiltrative lymphocytosis syndrome (DILS), a condition typified by a penetration of constant CD8 cells lymphocytosis that results in swelling of the gland[4,28].

DiGiuseppe *et al*[32] postulated persistent generalized lymphadenopathy to be a cause of benign lymphoepithelial lesions in parotid gland. An increased viral load is also known to be associated with salivary gland enlargement by altering the expression of strategic cellular genes[33]. Ihrler *et al*[30] had demonstrated a secondarily lymphoid penetration of parenchymal component of the salivary gland that induces a lymphoepithelial reaction of striated salivary gland ducts. Owotade *et al*[34] had reported 5 cases of parotid gland enlargement and had managed them with different modalities like Fine needle Aspiration, Anti-retroviral therapy and parotidectomy.

The conditions that can simulate lymphoepithelial cysts are salivary gland duct retention cyst (mucocele), mucosa associated lymphoid tissue lymphoma that may possess cystic constituent and polycystic parotid disease[35]. The possibility of papillary cystadenoma lymphomatosum should also be excluded in these patients[36].

RANULA

The involvement of ranula as an oral manifestation in HIV patients has been suggested which still has not been established. However, Syebele *et al*[37] had demonstrated a mixed and delayed response (3-6 mo) of ranulas for regression to HAART. The precise etiopathogenesis of the association amongst these dual dissimilar pathological conditions is ambiguous. Chidzonga *et al*[38] had documented a high prevalence rate (88.5%) of HIV subjects within a cohort of 38 patients with sublingual ranula. A case report documented that without any surgical intervention, sublingual mucocele had entirely lapsed after initiation of HAART[39]. Syebele *et al*[39] had also proposed research on association between ranulas and HIV infection to establish the likely result of HAART on ranula. Case control studies are required to evaluate the degree of periductal lymphocytosis, isolation of viral particles and chemical analysis of the mucus present in ranula[40].

SALIVARY GLAND NEOPLASMS

Patients with HIV/AIDS demonstrate augmented possibility of malignancy, predominantly viruses triggered cancers[41]. The greatest risk for salivary gland carcinoma was found to be lymphoepithelial carcinoma, which is

an undifferentiated carcinoma associated with Epstein Barr virus and also having a prominent non-neoplastic lymphoplasmacytic infiltrate[41]. The most common site of involvement is parotid gland. The common histological subtypes of salivary gland malignancy like mucoepidermoid carcinoma and adenoid cystic carcinoma seen in general population are not commonly seen in HIV patients[41]. High grade Non-Hodgkin's lymphoma and Kaposi's sarcoma are the other frequent malignancies associated with salivary glands in HIV patients[42]. The greater probability of squamous cell carcinomas of both nasopharynx and salivary glands could be ascribed to tobacco or alcohol usage, which are frequent in HIV subjects and related to other malignancies in the head and neck region[43]. Rare case reports of primary squamous cell carcinoma affecting Stensen's duct and developing from Cheilitis glandularis were documented in subjects infected with HIV[44,45].

HIV-ASSOCIATED SIALADENITIS AND SICCA COMPLEX

In a study conducted in 2009 in 105 AIDS patients the researchers found the most common infectious conditions affecting the sublingual and submandibular glands were mycobacteriosis followed by cytomegalovirus (CMV) and cryptococcosis[46]. HIV p24 was observed in lymphocytes and macrophages correspondingly[46]. The highest prevalence of cells seen in chronic nonspecific sialadenitis were CD8 lymphocytes, while CD68 macrophages were predominant in the mycobacteriosis-associated granulomatous and nonspecific diffuse macrophagic sialadenitis[46]. Parotid gland histopathological changes were observed in more than half of the HIV infected patients in a research conducted by Vargas *et al*[47]. Chronic sialadenitis of non-specific origin (29 cases) was the frequent change observed followed by various conditions of infectious origin (22 cases). Amongst the infectious conditions, 10 patients had Mycobacteriosis, followed by nine patients with cytomegalovirus infection, cryptococcosis in three patients and lastly histoplasmosis in two patients[47]. Wax *et al*[48] had reported three patients of CMV sialadenitis who clinically had nodules in parotid gland in HIV/AIDS patients. A possible complication of sialolithiasis in HIV positive patient with the usage of HAART drug atanavir was suggested[49].

SALIVARY GLAND DISEASE IN CHILDREN

HIV positive children often present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of lymphoid hyperplasia predominated[50]. Parotid gland enlargement is a common condition found in pediatric patients with HIV infection. In the pediatric HIV population, its prevalence is 1% to 10%[51]. DILS or Sjogren syndrome- resembling condition, first seen in pediatric HIV infection, is a CD8 lymphocyte facilitated syndrome that might involve the submandibular as well as parotid salivary glands[52]. HLA-DR11 and HLADR5 have been associated with salivary gland enlargement in HIV infected children signifying a possible genetic predilection[53].

RECENT ADVANCES IN RESEARCH AND MANAGEMENT OF SALIVARY GLAND DISEASE

More studies need to be done for exact association between HAART and hypo salivation. Longitudinal studies documenting xerostomia need to be done measuring the salivary flow subjectively prior to HAART and after HAART. There should be more research on the role of Ranula as an oral mucosal finding in HIV patients. Artificial salivary glands are also being formulated[54]. HAART's success has resulted in patients with xerostomia, a risk factor for caries and its potential sequelae, thus affecting the patient's quality of life.

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