Salivary Gland Disease in Pediatric HIV Patients: An Update

Andres Pinto, DMD Scott S. De Rossi, DMD

ABSTRACT

Oral manifestations are one of the earliest clinical indicators of HIV infection and progression in children. Prompt recognition of these signs and symptoms by dental providers can help in the diagnosis and intervention of delaying the progression of HIV disease to AIDS. Salivary gland disease is a common manifestation of HIV infection in pediatric patients, presenting either as gland enlargement and/or xerostomia. The parotid glands by far are most frequently affected, though the other major glands are commonly involved. Diseases of the salivary glands and the corresponding quantitative changes in saliva affect the homeostasis of the oral cavity and account for significant morbidity during the progression of HIV disease. This paper summarizes the research on HIV-related salivary gland disease and outlines treatment and management considerations. (*J Dent Child*. 2004;71:33-37)

KEYWORDS: SALIVARY GLAND DISEASE, HIV INFECTION, CHILDREN

The oral manifestations of HIV infection in the pediatric population have been thoroughly described in the literature. Salivary gland dysfunction can lead to increased caries rate, chronic sialadenitis, and periodontal disease. It is classified as either glandular enlargement and/or xerostomia in children an adults.[1,2]

SALIVARY GLAND ENLARGEMENT

Salivary gland enlargement (SGE) was a common oral manifestation in HIV positive children before the era of highly active antiretroviral therapy (HAART). Prevalence of salivary gland dysfunction in HIV positive individuals varies considerably (0% to 58%), depending on the population studied and methods used to assess dysfunction.[1,3-10] The parotid glands are most commonly affected,[11-13] followed by the sublingual and submandibular glands. The etiology of the glandular enlargement is not known and may be associated with pain and xerostomia. SGE in the pediatric AIDS group is characterized by slow continuous enlargement of the gland causing facial asymmetry.[14] Parotid enlargement has been linked to generalized lymphoadenopathy and lymphoid interstitial pneumonitis (LIP), occurring between 4 months to 4.5 years of age.[14-16] Although the exact pathophysiology remains uncertain, theories concerning the origin of SGE include lymphoepithelial lesions,[17,18] cysts involving the salivary parenchyma, interglandular lymph nodes, and an inflammatory infiltrate similar to that seen in Sjogren's syndrome.[14] Greenspan described the possible relationship between SGE and T-lymphocyte CD8+ cell infiltration in the gland.[9] In addition, genetic loci have been linked to SGE in children, specifically HLA DR5 and HLA-DR11, suggesting a genetic predisposition to this condition.[19]

Lymphoepithelial cyst formation, caused by the obstruction of the salivary ducts from lymphatic nodes that are entrapped during the glandular formation, can lead to gland enlargement. This is an infrequent cause of gland enlargement in children, although there are several cases reported in the literature of lymphoepithelial lesions developing in HIV positive children.[17,20] Ultrasound, computer tomography, and MRI imaging of patients with enlarged salivary glands is often necessary. The list of pathologies with similar appearances upon radiographic exam includes polycystic parotid disease, Warthin's tumor, gland abscess, Sjogren's syndrome, and lymphoma. The inflammatory reaction observed in salivary glands does not appear to be restricted to the major glands. Studies have shown biopsies of minor salivary glands to have an increased focus score (defined as a histologic classification for lymphocytic infiltration, similar to Sjogren's syndrome).[21]

The role of a viral etiology in SGE has been discussed in the literature.[22] Epstein-Barr virus (EBV) and cytomegalovirus (CMV) have primarily been considered as the agents most likely responsible for salivary gland disease, although multiple

Dr. Pinto is director, Medically Complex Patient Care; Dr. De Rossi is director, Residency Program in Oral Medicine, Department of Oral Medicine. University of Pennsylvania, Philadelphia, Penn.
Correspond with Dr. Pinto at apinto@dolphin.upenn.edu

studies have failed to show evidence of these viruses in SGE.[22,23]

The diffuse infiltrative lymphocytosis syndrome (DILS), described by Itescu,[16] is characterized by lymphocytosis and visceral lymphocytic infiltration, affecting the salivary glands and lungs (lymphocytic interstitial pneumonia). The diagnostic criteria for DILS includes HIV seropositivity documented by enzyme linked immunoassay (ELISA) and Western Blot, bilateral SGE, or xerostomia persistent for more than 6 months, and histologic confirmation of salivary or lacrimal glandlymphocytic infiltration in the absence of granulomatousor neoplastic involvement. Most importantly, patients who carry a diagnosis of DILS have a 4-fold risk of developing non-Hodgkin's lymphoma.

If a patient has dry eyes and mouth accompanied by SGE similar to that with Sjogren's syndrome, a full workup for connective tissue disease or other immune deficiencies should be performed. Occasionally malignant lesions are associated with SGE. Recently, 2 cases of parotid mucosa associated lymphoid tissue (MALT) lymphoma arising from an enlarged parotid gland have been documented.[24,25] On CT imaging, this entity resembled the lymphoepithelial cyst anatomy, but in MALT the cyst presentation was more florid. Other systemic conditions related to SGE are anemia and hypergammaglobulinemia.

The diagnostic workup of SGE in HIV positive children should include CT or MRI. The use of ultrasound in the evaluation of SGE has been proposed as an alternative to conventional imaging and as a good screening option for malignancy.

ACUTE AND CHRONIC PAROTITIS

Parotitis is an infrequent complication of pediatric AIDS, although when related to gland enlargement, it is considered a positive predictor for long-term survival.[26] Flanagan[3] found a 3% incidence of parotitis in a group of perinatally infected children. These findings have been reported in the later stages of the disease and patients with parotitis have demonstrated a slower progression to AIDS.[26] Suppurative parotitis is a very uncommon complication of HIV disease in children. When present it usually affects infants and neonates. The offending microorganisms include *staphylococcus aureus* and less frequently *e coli* and *pseudomonas aeruginosa*. Viral parotitis has been linked to CMV and paramyxovirus. Predisposing conditions for parotitis include dehydration, malnutrition, oral trauma, immune deficiency, sialolithiasis, and medications that can cause xerostomia.[27,28]

XEROSTOMIA AND SALIVARY GLAND HYPOFUNCTION

In HIV pediatric populations, the prevalence of xerostomia reaches 16% to 20%,[29] with almost a 50% reduction in flow with respect to control age and sex matched groups. More recent studies in pediatric patients, however, showed a much lower prevalence of xerostomia, ranging from 1% to 6%.[2,30,31] This discrepancy could have been in part due to the improvement of antiviral regimens and the advent of effective combined HAART.[26,32,33] Parotid swelling does not necessarily correspond with xerostomia.[9,11,13] Some studies have detected concurrent xerostomia in children with gland enlargement, but very few have actually measured salivary flow rate in pediatric HIV/AIDS. Ramos-Gomez et al,[4] reported no difference in stimulated salivary flow between HIV and control children, although no reference was made specifically to the relationship between patients with gland enlargement and salivary flow. Patients suffering from the Sjogren-like syndrome demonstrated decreased stimulated parotid flow rates. Other studies have reported a decrease in stimulated salivary flow, but unstimulated rates remained unchanged.[21] Bretz et al compared salivary flow rates of 447 children located in North and South America to demographic parameters finding no significant changes.[34]

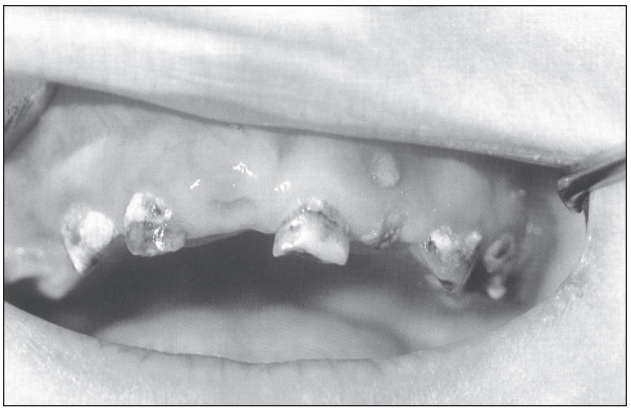

Figure 1. Rampant caries secondary to severe xerostomia.

No specific association has been found between measured salivary flow and presence of caries in HIV positive children. Interestingly, some studies have demonstrated elevated stimulated flow rates in HIV patients when compared to controls.

The susceptibility to caries in HIV pediatric infection remains controversial. Some authors back the theory of increased susceptibility secondary to general and local immune suppression and diminished salivary output,[7] while others do not find any variation when compared to control groups.[35-37] Overall it appeared that children with more advanced HIV disease showed a higher caries rate (Figure 1). The cause was multifactorial, including high sucrose containing medications, diet, salivary gland disease, and immune suppression.

Ramos-Gomez et al described a classification and presented diagnostic criteria for the common oral manifestations of pediatric HIV infection. Salivary gland dysfunction was placed in group 1 (lesions commonly associated with pediatric infection) demonstrating the frequency with which pediatric AIDS patients developed salivary gland problems.[4] Salivary flow rates were most likely related to the degree of inflammatory infiltrate in the glands, but did not appear to be associated to the degree of immune suppression.[26]

A clear link exists between the presence of xerostomia and the occurrence of candida. By far, candidiasis is the most common oral manifestation of HIV disease and AIDS (Figure 2). With the advent of HAART, the incidence of candidiasis has decreased due to the maintenance of a minimum level of immunocompetency. As with adult HIV

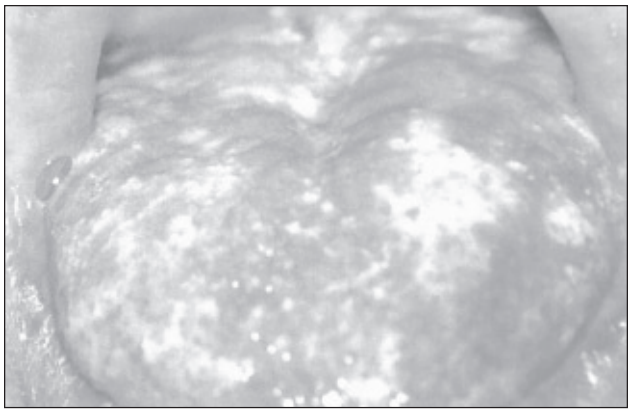

Figure 2. Oral candida infection (tongue dorsum). Reproduced with permission from* Color Atlas of Oral Diseases in Children and Adolescents*. Laskaris G, Georg Thieme, Stuttgart, Germany, 2000.

patients, 4 clinical presentations of candida are observed: pseudomembranous, erythematous, hyperplastic, and angular cheilitis. As salivary flow is diminished the frequency of candidal infections increases.

TREATMENT OF SALIVARY GLAND DISEASE AND DENTAL MANAGEMENT CONCERNS

The pediatric dentist should be aware of the possible complications of salivary gland disease in the pediatric HIV/AIDS population. Often the salivary gland disorders or their potential sequelae can be a predictor of HIV disease progression. Consultation with the child's infectious disease provider, including ordering complete blood counts, should give the practitioner an indication of the child's immune status. Assessment of salivary function should be performed during an initial dental exam. Subjective complaints of dryness in children are often equivocal, so the clinician should be familiar with examination of the Stensen's and Wharton's ducts to verify flow. Palpation of the major glands and milking of the major glands should be a standard part of the comprehensive head and neck examination of the HIV Positive pediatric patients. As mentioned earlier, salivary gland disease can present as benign enlargement with or without xerostomia, xerostomia alone, or parotitis, or more ominous conditions such as malignancy (Figure 3).

PAROTITIS

Serious complications in children related to infections of the salivary glands can become life threatening at a faster rate than in adults. Therefore, management of infections includes aggressive antibiotic therapy and fluid balance to avoid dehydration. Dental management of parotitis includes emphasizing the importance of adequate hydration and aggressive antibiotics. The pediatric dentist should be aware of the possible etiologic agents that can cause parotitis (bacterial/viral). Previous knowledge of the child's immune status serves as a guide toward diagnosis (ie, cytomegalovirus or paramyxovirus in immune-compromised children). Thorough examination of salivary ducts can provide valuable information about the etiology of the infection (purulence in saliva, thickmucous saliva) and guide the clinician to adequate treatment. The antibiotic of choice is clindamycin, in a dosage of 8-25 mg/kg/day. Another antibiotic that can be considered as a therapeutic alternative is penicillin, considering the gastrointestinal side effects of clindamycin.

SALIVARY GLAND ENLARGEMENT

Enlargement of the salivary glands is often left untreated. Close observation is the mainstay of treatment, once other factors of enlargement (eg, malignancy) have been ruled out. Most cases of SGE will show regression when antiretroviral therapy is implemented.[35,38] This applies for asymptomatic cases with absence of salivary dysfunction. Doxycycline sclerotherapy has been described as an effective treatment reducing the size of the glands in up to 50%.[39] Radiation therapy has been effective in reducing glandular size in adults, but carries a high risk for malignancy in children. The use of steroids has not proven beneficial in reducing SGE and has had severe side effects in young patients. Surgical treatment for SGE is mainly esthetic when the enlargement interferes with daily activities. This approach consists of partial gland resection or ablation and is reserved for only the most severe and disfiguring cases.

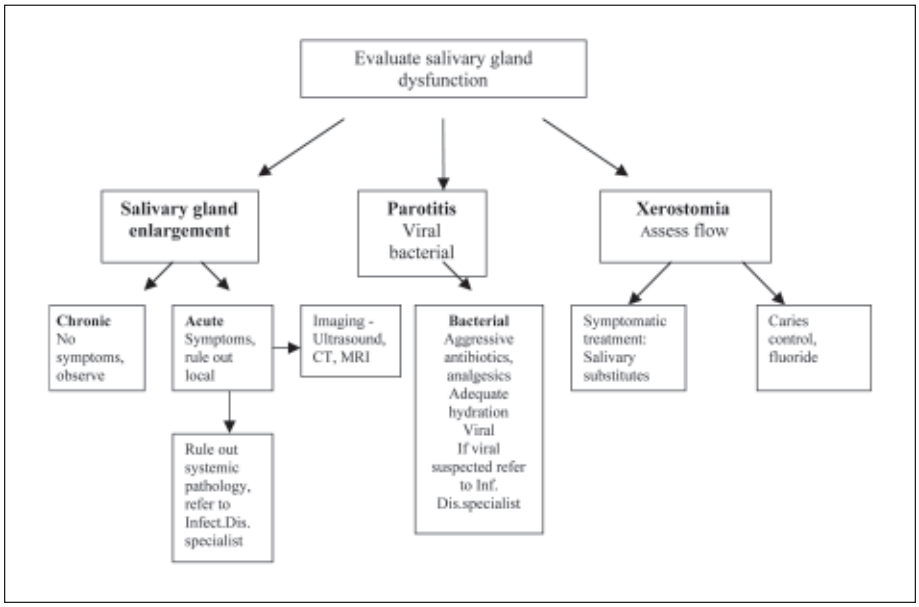

Figure 3. Recommendations for the evaluation and management of HIV-related salivary gland disease in children.

XEROSTOMIA AND SALIVARY GLAND HYPOFUNCTION

The mainstay of treatment for xerostomia in pediatric patients remains palliative, including the use of hydration and topical oral moisturizers. Several prescription saliva replacement formulations are available. Their use is limited to patients with severe dryness and consists of rinsing with the artificial saliva as needed during the day. The safety of systemic therapies such as sialogogues in pediatric patients has not been well established. The 2 currently used cholinergic agents, pilocarpine and civemeline, have not been approved for use in the pediatric population. Children with xerostomia require an aggressive oral hygiene protocol, anticipatory guidance, implementation of fluoride treatments as necessary (twice a year as a minimum) and caries control. Use of fluoride trays might be considered with severe hypofunction. Recall visits should be scheduled every 3 to 4 months in children with salivary dysfunction due to their increased susceptibility to caries.

Management of candida infection can be achieved with topical antifungal rinse (Nystatin 1:100.000 solution). The recommended dosage is 5 mL rinse and expectorate 3 to 5 times a day. Infants or individuals with impaired swallowing need to have the rinse suctioned from their mouth. For children with recalcitrant candidiasis, systemic therapy can be implemented in consultation with the child's infectious disease physician. Ketoconazole, a popular systemic antifungal, can be hepatotoxic and liver enzyme levels must be monitored in patients taking these medication.

When progressive glandular enlargement is evident, function has to be confirmed by milking the involve gland and observing flow. If minimal or absent flow is seen, further flow studies might give an objective assessment of function loss. Purulent discharge from the ducts suggests acute infection and appropriate treatment should be administered. If the SGE is acute, the workup should include ruling out a tumor, infection (viral or bacterial) or sialolithiasis. Asymptomatic enlargement should be monitored and salivary flow assessed during recall visits.

CONCLUSIONS

Salivary gland disease in the pediatric HIV population remains an important oral manifestation of HIV disease and AIDS. Often, certain types of salivary gland disorders or their sequelae provide important information regarding the progression of HIV disease. Proper history and examination by the clinician can detect the presence of SGE and xerostomia leading to appropriate treatment improving the overall well-being of these patients.

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