Salivary Abnormalities in Dentistry

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Overview

Dentists are involved with aspects of salivary gland function in several ways, such as diagnosing problems involving the major and minor salivary glands, in the management of oral dryness associated with salivary problems, in the treatment of caries and periodontal disease resulting from decreased salivary flow, and in controlling salivation during restorative procedures. Significant abnormality or disease of the salivary glands, such as that associated with Sjögren syndrome or neoplasm, necessitates additional evaluation by an otolaryngologist or an otolaryngologist/head and neck surgeon for comprehensive treatment of the gland pathology itself. However, a general dentist may be called upon to provide follow up in terms of management of the patient's subsequent oral health.

In some countries, maxillofacial surgeons are also involved in the primary treatment of neoplasm involving the salivary glands.[1] This article reviews basic salivary anatomy and physiology, several important diseases affecting the glands, salivary constituents as measures of health, trends in diagnosis, and the management of xerostomia and drooling.

Salivary Gland Anatomy

The salivary system is composed of 3 major gland sets and multiple minor glands. At rest, the parotid glands, located anterior to the ears, produce approximately 25% of oral saliva. The submandibular glands, in the floor of the mouth, produce 70%. When stimulated, the parotids then produce approximately 50% of the whole saliva volume. The sublingual glands, under the tongue, produce about 5% of the total oral saliva. Approximately 1000 minor glands, localized to the cheeks, lips, and other intraoral mucosa, contribute about 7% to the whole saliva volume. The resting flow rate of whole saliva has been shown to be greater in men than in women (0.1-0.2 mL/min).[2]

Saliva is primarily water but does vary in viscosity depending on the gland that produces it. The parotids produce the most fluid saliva, as they are composed of serous acini, with the sublingual gland producing mucus from mucous acini. The submandibular glands produce both serous and mucous saliva. The minor glands are primarily mucous producing, except those under the tongue, which produce serous fluid. Saliva contains a number of components, including various electrolytes, glycoproteins, enzymes, and mucus, as well as secretory immunoglobulin A, lactoferrin, lysozyme, and peroxidase—with the latter 4 components important in that they exhibit antibacterial activity.[3] Additional elements of the saliva, which may have potential prognostic significance, include epidermal growth factor, salivary glucose, cortisol, and progesterone.[4] Approximately 1-1.5 liters of saliva are produced by the glands in a day.

Autonomic innervation of the salivary glands involves both parasympathetic and sympathetic input. Parasympathetic stimulation prompts high flow with a low glycoprotein content, and sympathetic activity prompts a low flow rate and saliva that is more viscous because of increased protein and glycoprotein content. A number of different cellular signaling and regulatory systems in the acini and ducts are involved with saliva formation when the glands are stimulated by gustatory, masticatory, and psychic stimulation.

Salivation and Age

It was once thought that salivary function did not change significantly with age. However, prior research included only a limited number of longitudinal studies[5] and the results were considered contradictory. It was generally believed that parotid flow rates were age-stable in healthy people.[6]

More recent research, however, suggests that salivary function in the major glands may diminish with increasing age.[7] For example, in a cross-sectional, population-based cohort study of 1130 subjects by Dodds et al (2005),[7] age-related decline in saliva output was found to occur in the stimulated parotid, unstimulated submandibular/sublingual, and stimulated submandibular/sublingual glands. Additional research suggests that changes may occur in the viscoelasticity of saliva with aging, particularly in saliva produced by the submandibular and sublingual glands.[8]

In contrast to the above, at least one recent study suggests that the stimulated whole saliva flow rate (from eating meat or chewing paraffin) may not be significantly impacted by age.[9]

Age-related flow rates within the minor glands vary depending on location. Within the palatine glands, a flow rate change with aging does not seem apparent; however, in the labial glands, flow has been found to diminish over time.[10]

Evidence also suggests that the constitutional components of saliva may vary with age. For example, in a study of 127 healthy subjects ranging in age from 20-81 years, the mean concentration of nerve growth factor was found to diminish with increasing age in submandibular gland saliva.[11] Histatins, which have antifungal properties, have also been shown to decrease with age.[12] The population-based study of Dodds et al also demonstrated alterations in saliva components with age.[7]

Histomorphometric parameters of age-related gland size, based on CT and postmortem data and flow rate analysis, have shown a significant reduction in size and cellular components over time, consistent with altered salivary output.[13] Changes observed by Azevedo et al include acinar atrophy, fibrous or adipose replacement in the gland parenchyma, oncocytosis, congested blood vessels, ductlike formations, and mononuclear infiltrates.[14]

Diagnosis of Dry Mouth

Salivary flow rates have been evaluated in multiple studies over the last 50 years. Data clearly indicate that the unstimulated flow rate of whole saliva varies considerably among individuals, between men and women, with age, and in relation to confounding oral disease.[15]

Another important factor in defining dry mouth is the relationship between the sensation of oral dryness and the actual flow rate of saliva, which can be vastly different. As pointed out by Fox et al 1987,[16] the perception of dryness may not correlate with what are considered normal low flow rates. Many individuals reporting oral dryness do indeed have low resting whole saliva volumes, yet in some cases, the patients with low flow rates do not experience (ie, report) dryness, and, even more perplexing, some patients who have normal resting saliva report oral dryness. This suggests that dryness is a perceptual sensation not necessarily related to actual flow volumes. Limited evidence suggests that when a patient's resting saliva volume falls to half its normal baseline value, there can be a perception of oral dryness (even if this value is above the normal range for resting saliva).[17]

Additional factors that may confound the sensation of oral dryness include the clearance of accumulated saliva and saliva-film thickness associated with different oral structures (eg, hard palate, lips, tongue).[18]

One of the more helpful clinical subjective guides for determining oral dryness arises from the work of Thomson and colleagues (1999).[19] As a result of their work and the preceding work of others, an 11-item questionnaire, with each question scored based on a 1-5 ordinal scale (never = 1, hardly ever = 2, occasionally = 3, fairly often = 4, and often = 5), was developed. Based on their analysis of accumulated data, the greater the total score, the more likely it is a patient has xerostomia. The questionnaire items are as follows:

- My mouth feels dry.
- My lips feel dry.
- I get up at night to drink.
- My mouth feels dry when eating a meal.
- I sip liquids to aid in swallowing foods.
- I suck sweets or cough lozenges to relieve dry mouth.
- My throat feels dry.
- The skin of my face feels dry.
- My eyes feel dry.
- I have difficulties swallowing certain foods.
- The inside of my nose feels dry.

As noted previously, defining xerostomia based on resting and stimulated salivary flow may be problematic because of the many potential confounding factors. Nonetheless, as a general rule, 0.7 mL/min is the value considered the cutoff point for estimating normal versus abnormal stimulated flow. More information regarding the technique for whole salivary flow assessment and the relative values related to normal unstimulated and stimulated whole saliva flow is found in the section on Sjögren's syndrome.

Other subjective complaints that patients with dry mouth may report include difficulty with speech, loss of taste, and frequent oral infections (eg, candidiasis) and mucosal trauma. These problems may lead to considerable problems (and in some instances significant pain), coupled with dysfunction during the patient's attempt to masticate.

Objective findings are numerous. Lack of saliva causes drying of the intraoral mucosa. When this occurs and is chronic, oral tissue becomes atrophic and either erythematous or pale. It is easily injured. The tongue can be atrophic and, in severe cases, is inflamed and fissured, possibly with loss of filiform papilla. Oral dryness can lead to secondary infection, typically fungal infection (eg, oral candidiasis), which can cause oral burning. Typically, an increased prevalence of dental decay occurs, primarily involving the root surfaces or the teeth, including the anterior mandibular teeth, which are usually quite resistant to caries. Acute

dryness associated with a variety of parotid and submandibular conditions may be associated with facial swelling and glandular pain at rest and with palpation.

Salivary Gland Disease

A primary consideration in the dental treatment of elderly patients is the effect of the many common conditions that can occur, including Alzheimer disease and Sjögren syndrome, on salivary function, as well as the effect of nonprescription and prescription medications that may be used to treat a wide range of age-related diseases that do not otherwise alter salivation.

Xerostomia has also been associated with smoking, mouth breathing, and aging, as well as sleep, although the clinical effect of dryness occurring at night is relatively mild. It may also occur as a result of dehydration, emotional stress, local surgery, and mechanical blockage. More significant dryness (and resulting signs and symptoms) is often caused by single-agent or multidrug therapy, connective-tissue disease, Sjögren syndrome, HIV infection, and radiation therapy. Other conditions associated with oral dryness include avitaminoses; diabetes; anemia; viral infection; congenital disease (eg, congenital aplasia of a gland or duct); and diseases such as lymphoma, sarcoidosis, and tuberculosis. Tumors that block a duct or ducts within a major gland can also produce oral dryness.

Sjogren Syndrome

Sjögren syndrome is a chronic condition that is termed primary if it is not associated with other autoimmune diseases or secondary if there is a comorbid disease, such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. Estimates vary with respect to prevalence, with reports that the condition affects approximately 0.5-1.4% of the US population. Because Sjögren syndrome involves not only the salivary glands (resulting in oral dryness) but also the lacrimal glands (resulting in xerophthalmia or dry eyes), it is also called sicca syndrome.[20]

For an extensive review of Sjögren syndrome and the American-European classification criteria, including, among other factors, positive minor gland biopsy findings, see Sjogren Syndrome.[21] The dental contribution to the diagnosis of Sjögren syndrome thus not only includes recognition of the signs of the disease (ie, enlarged parotids, associated symptoms of eye and mouth dryness), but also may include a request by an otolaryngologist for a minor gland biopsy.

Minor gland biopsy is not without controversy, primarily because it might be unreliable in predicting disease, particularly in elderly persons. This may partly be related to incorrect interpretation of the pathologic criteria that have been established for identifying the condition.

In a study by Langerman et al (2007),[22] clinical and pathologic data from 47 patients referred with a suspected diagnosis of Sjögren syndrome, established by the presence of extraglandular features including joint and nervous system involvement, were reviewed. Scoring of the gland tissue specimens was based on current grading criteria. The authors found incorrect interpretation of the tissue specimens because the grading system was not applied appropriately by the evaluating pathologist. Ten percent of the tissue samples (5 specimens) represented pathologic misdiagnoses and, in 16 (34%), no diagnosis could be confirmed. When the gland tissue was reassessed using a more consistent interpretation of the grading criteria, 29 (62%) were definitively positive and 17 (36%) were negative. However, in this retrospective study, a positive biopsy was not predicted by the presence of positive serology or sicca symptoms.

Evidence also suggests that the sensitivity and specificity of minor gland biopsy may be improved by using a cumulative focus score (cFS), which is taken from interpretation of 3 slides with tissue cut at 200-µm intervals. This score is substituted for the baseline focus score defined by the American-European Consensus Group (AECG) criteria.[23] A Japanese study suggests the AECG offers acceptable reliability.[24]

However, the AECG appears to vary considerably with respect to disease prediction. The literature suggests that the sensitivity of minor gland biopsy using the AECG standard pathologic interpretation varies from 38-82%, with specificity ranging from 85-94%.[25, 26] At least one author has suggested that lip biopsy may not be necessary when there is a confirmed abnormal serology (anti-Sjögren syndrome A/anti-Sjögren syndrome B), as this finding is highly predictive of a positive pathology interpretation.[27] In one interesting interpretation of the results comparing parotid biopsy with lip biopsy, the authors of a study comparing gland biopsies conclude that lip biopsy may be associated with greater morbidity than parotid biopsy.[26]

As minor glands are plentiful in the region of the lower lip, this is the best location for harvesting these organs. They can be readily demonstrated by pulling the lip out and down. This maneuver reveals small bumps, which reflect the underlying glands. In the typical biopsy, following delivery of local anesthetic, a 1.5- to 2-cm incision is made parallel to the vermilion border in the labial mucosa lateral to the midline. (A vertical incision should be avoided as it may sever nerve tissue.) Multiple glands are readily exposed following the incision. Each gland can be easily removed by grasping it with cotton pliers, gently pulling it up, and incising its

base with the scalpel. The incision should be tightly sutured to avoid exposure of remaining glands via mouth movement.

It is recommended that at least 4 minor glands be removed for histopathologic examination. Excised glands submitted to pathology are examined for the presence of focal lymphocytic infiltration, including plasma cells occurring adjacent to normal acini (per AECG criteria). For a good description of the full clinical technique, including appropriate photos, see Lip Biopsy.[25]

In addition to a biopsy, it may also be useful to confirm xerostomia by assessing the relative volume of saliva via sialometry. Volume can be determined by weighing the volume of whole saliva collected from the glands over 5 minutes when they are initially unstimulated and then when the glands have been stimulated using a small (0.5-cm) oval of wax (or a tasteless gum base – 1 chew stroke/second) that is masticated by the patient. Saliva is deposited into a graduated test tube, which is weighed prior to and after the procedure. The volume of unstimulated whole saliva considered normal is 0.25-0.50 mL (or gram)/min. Visible dryness may not be observed until the level falls below 0.10 mL (or gram)/min. For stimulated whole saliva, flow rates considered normal range from 1-3 mL (or gram)/min.

Unfortunately, this volume test does not help to differentiate diagnoses, but it may be useful in defining the patient's response to subsequent treatment. In the research environment, a "cup" can be applied to the ducts of the glands for direct flow measurement of the fluid coming from each gland. Primary research reveals that in Sjögren syndrome, salivary sodium, chloride, lactoferrin, and immunoglobulin A are elevated, but these changes are nonspecific for the purpose of diagnosis.

Secondary Sjögren syndrome

Sjögren syndrome can also arise in association with other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective-tissue disease, relapsing polychondritis, or polymyositis.[28] Dental disease and dental management of the patient with primary or secondary Sjögren syndrome may also be complicated by secondary disease–related factors, including fatigue, cutaneous vasculitis, myalgia, arthralgia, myositis, liver disease, nervous system inflammation, kidney disease, bruising, leukopenia, thrombocytopenia, and anemia.

Salivary Gland Tumors

Tumors involving the salivary glands are not uncommon and can involve both the major and minor glands.[29, 30] In an institutional review of 244,204 cases assessed by the pathology department of a Turkish hospital between 1994 and 2005, 235 (0.09%) cases of salivary gland neoplasms were identified.[31] The female-to-male ratio covering this 12-year period was 1.04:1, and the mean age of patients was 47 years. Most lesions (67.66%) were found in the parotid gland, with 14.47% localized to the submandibular gland and 17.87% in the minor glands. Of these tumors, 62.13% were found to be benign, while 37.87% were malignant. The most common benign tumor was the pleomorphic adenoma (41.70%), and the most common malignancy was mucoepidermoid carcinoma (11.49%). These percentages are roughly similar to those reported elsewhere.[31] Another important malignant tumor that can occur as a seemingly innocuous subepithelial nodule is adenoid cystic carcinoma of a minor salivary gland.

Minor gland salivary tumors are most frequently found on the posterior lateral hard and soft palates, with the lips the second most common site of occurrence. Relative risk of malignancy appears to be related to where a lesion is located. For example, 91% of tumors in the retromolar region and a large percentage in the floor of the mouth are found to be malignant. In addition, recurrent salivary gland cancer is considered high risk and necessitates aggressive multimodality treatment.[32] Neville et al extensively cover the many diverse types of benign and malignant tumors that can occur within the salivary glands.[20]

Risk factors associated with the development of salivary gland cancer are not fully defined but may include smoking; prior radiation treatment for tinea capitis, enlarged tonsils, enlarged thymus glands, or skin disease; prior dental radiography (taken in the past when exposure levels were excessive)[33] ; prior bone marrow transplantation[34] ; history of lip cancer in men[35] ; age and sex[36] ; lymphoid organization of minor glands[37] ; and radiotherapy for Hodgkin lymphoma (mucoepidermoid carcinomas and adenocarcinomas).[38]

A study that evaluated the possible linkage of BRCA gene mutations and salivary gland cancers reported that individuals who carry BRCA mutations face an increased risk for salivary gland cancer. The authors also added that these results warrant further investigation into the nature of a possible linkage between germline BRCA mutations and salivary gland cancer.[39, 40]

Cellular phone use has also been implicated in the etiology of parotid gland malignancy.[41] However, in a case-controlled study of 69 patients with salivary gland tumors (63 with a parotid gland tumor) and 262 randomly recruited controls using "unconditional" logistic regression adjusted for age at diagnosis, sex, year of diagnosis, and socioeconomic index, it was found that cell phone use was not associated with an overall increase risk of salivary gland tumors or an increased

risk based on phone type or cumulative use. The authors conclude that light-to-moderate cell phone use does not appear to constitute a significant risk for tumor development.[42]

It is recognized that tumors of the submandibular glands have a worse outcome post treatment than tumors involving the parotids. This is primarily because they tend to be adenoid-cystic carcinomas and mucoepidermoid or adenocarcinomas, which are highly invasive.

As a general rule, if during palpation of the salivary glands a nodule is detected during the facial component of the dental examination or if there is facial nerve palsy or reported ear pain and sensory loss within the second and third divisions of the trigeminal nerve (coupled with a palpable mass), it should be assumed that the detected abnormality is potentially malignant. These clinical features necessitate immediate referral for additional imaging and physical evaluation, particularly since disease prognosis appears to be highly dependent on tumor size and clinical stage.[43, 44] This may also be important with respect to nodules appearing to be associated with minor glands, even though most of these minor gland enlargements likely represent benign disease.[45]

Also see Salivary Gland Tumors, Major Benign; Salivary Gland Tumors, Minor Benign; and Salivary Gland Neoplasms.

Nonmalignant Salivary Gland Conditions

Other salivary conditions that may be encountered in clinical practice include congenital aplasia of a gland or duct, sialosis (sialadenosis), sialadenitis, sialolithiasis, and minor salivary gland problems, including mucocele, ranula, and necrotizing sialometaplasia.[46]

Congenital gland/duct aplasia

Salivary gland and duct aplasia are congenital diseases that can occur during development. These problems are very rare, but one or multiple glands may be involved. In cases in which there is significant absence of glandular tissue, xerostomia can be a problem. Salivary aplasia may occur with additional lacrimal gland aplasia or hypoplasia. In addition to oral dryness, symptoms may also include oral inflammation, dental caries, and dental erosion.

Sialosis (sialadenosis)

Sialosis primarily involves enlargement of the major salivary glands, with the parotids most frequently involved. Although sialosis is considered idiopathic, it may occur with advanced liver disease (alcoholic liver disease and alcoholic cirrhosis[47]), diabetes, nutritional deficiency,[48] and bulimia.[49] Although very rarely, sialadenosis may also occur as an adverse reaction to medication.[50]

In a group of 300 patients with liver disease, sialadenosis was found in 9.3% of subjects.[51] Some of these patients had alcoholic cirrhosis, but no significant association was noted between alcoholic cirrhosis and sialosis. Gland enlargement is symmetric, painless, and bilateral. The glands are soft to palpation and without pain. The condition is benign but may be unaesthetic. The histology of the involved glands reveals significantly enlarged acini, possibly with differences in the ultracytochemical composition based on the underlying disease (eg, bulimia vs diabetes)[52] and ultrastructural changes.[53]

Sialadenosis in bulimic patients has also been reported to occur in the minor salivary glands of the palate, causing swelling that could be mistaken for other benign or less benign tumorlike diseases or a neoplasm.[54] These conditions include necrotizing sialometaplasia caused by salivary gland infarction, benign lymphoepithelial lesions, and salivary duct cysts such as mucoceles of the minor glands that occur with extravasation or salivary retention,[46] as well as neoplasms such as adenocystic carcinoma, pleomorphic adenoma, or mucoepidermoid carcinoma.[55, 56]

Sialadenitis

Sialadenitis, an inflammation of the salivary glands, can be caused by infection arising independently or as a result of ductal obstruction from salivary stones or neoplasm[37] ; alternatively, it may develop secondary to autoimmune disease or medical problems necessitating radiation therapy of the glands or an area in the region of the glands. The condition may be acute or chronic in nature.

Symptoms can include oral dryness, taste disturbance (from oral discharge), and facial (and dental) pain at rest or with eating/chewing; with concomitant infection, fever may be noted. Signs can include facial erythema over the gland or in the inferior jaw/neck, facial swelling, lymphadenopathy, jaw-opening limitation, and pain in the gland with palpation. In chronic cases, a cutaneous fistula may be present. Purulent material may be expressed from the oral duct with milking of the gland.[57]

Of particular importance to dentists is the differential diagnosis, because salivary gland inflammation or infection can cause pain at rest and with function that may be localized to the teeth or in the case of the parotidis, the

preauricular/temporomandibular joint (TMJ) region. In the latter situation, the patient may have jaw-opening limitation, which is also a sign reflecting a potential temporomandibular disorder (eg, TMJ dysfunction or myofascial pain and dysfunction).

When the above symptoms and signs occur, tooth and TMJ pathology must be ruled out by a thorough history and a comprehensive examination. This can include, in some cases, culture of the material expressed from the gland (if present and taken prior to antibiotic treatment) and, if symptoms suggest a more generalized bacteremia or general sepsis, a blood culture. If Sjögren syndrome is suggested, serum analysis should include an antinuclear antibody, anti-SS-A, and anti-SS- B, as well as an erythrocyte sedimentation rate. The clinician not confident in providing this level of expertise in working up a patient with possible sialadenitis should provide an appropriate medical referral.

Sialolithiasis

The submandibular glands, of all the salivary glands, appear to be most susceptible to the formation of calculi or salivary stones. Sialolithiasis is associated with pain and swelling in the region of the duct behind the stone; the pain is exacerbated by food intake. Stones in the region of the Wharton duct may be visualized at examination or via an occlusal radiograph and, sometimes, panoramic imaging.

Recommended treatment includes moist heat applied to the bland, milking or massage of the gland, increased fluid intake (noncaffeinated fluid), and sialagogues to stimulate salivary flow. The latter, however, may simply increase pain and swelling when there is a large obstruction. In this case, surgical removal may be necessary.

Sialolithiasis is of unclear etiology, although smoking and diuretic use have been implicated in its development.[58] In one study, a fishbone was found to be located centrally within the developed calculi.[47] Reoccurring infection is a potential problem with this condition.

Mucocele

The mucocele is the most common intraoral salivary lesion. The condition most often arises as a result of trauma to the mucosa and minor glands but can also develop secondary to blockage of a minor gland duct by a small stone. Mucoceles are typically small and transient in nature and last only days to weeks. More persistent, large, or reoccurring lesions can be problematic and may necessitate surgical removal of the affected minor gland. If the entire gland (and sometimes adjacent glandular tissue) is not removed, lesions may reoccur. Most mucoceles develop in the lower lip region, but they may also be found on other intraoral soft tissue where minor glands are present.[59]

Necrotizing sialometaplasia

Necrotizing sialometaplasia is a benign, noninfectious, inflammatory condition that presents most frequently as an erosive lesion of the palate.[60] Necrotizing sialometaplasia, involving destruction of minor salivary glands, also occurs less often on the retromolar area, buccal mucosa, tongue, and labial mucosa. Limited case reports also suggest that necrotizing sialometaplasia can occur in the parotid and submandibular glands.[61] Of importance to dentists, given its clinical presentation, it may be misidentified as a neoplasm, leading to unnecessary intervention. Trauma is thought to be the primary cause of necrotizing sialometaplasia,[62] although it has been associated with bulimia and vomiting.[63]

Lesions of necrotizing sialometaplasia, thought to be related to vascular necrosis, begin with submucosal swelling that quickly ulcerates, forming a large and fairly deep ulcer with slightly indurated and inflamed irregular borders. The size of a lesion can vary from one to several centimeters. The necrotizing sialometaplasia lesion heals spontaneously, and delayed healing (>5 wk) should heighten the clinician's suspicion of malignancy.[64] The differential diagnosis for a nonhealing lesion also includes lymphoma, Wegener granulomatosis, syphilis, and infection (deep fungal). Given the differential in cases of delayed healing, an incisional biopsy should be performed to confirm the diagnosis. Of interest, biopsy often speeds healing of a necrotizing sialometaplasia lesion.

Trends in Diagnosis

Salivary gland imaging

Although a few newer techniques may be useful in defining salivary gland pathology, standard plain film imaging continues to provide useful information for diagnostic purposes. The standard studies that can help in identifying salivary gland disease include the intraoral occlusal view (for viewing the submandibular ducts), the anteroposterior view, and the lateral or oblique jaw view.

Glandular ductal structure and gross soft tissue anatomy can also be evaluated via sialography. In this technique, a water-soluble material such as meglumine diatrizoate is injected into a duct and lateral, oblique, and anteroposterior plain films are obtained. (Sialography can also be combined with the newer cone-beam

CT [CBCT])

With sialography, the patency of a duct (eg, Wharton duct) is defined and the extent of gland arborization can be determined. If an obstruction is present, the injected medium does not penetrate the gland or a portion thereof, and filling defects are visualized. If chronic disease (chronic sialolithiasis) is present, it can be recognized by the presence of cherrylike ductal structures (suggesting retained secretions). Constriction of a duct suggests an inflammatory process, extravasation of material is thought to suggest Sjögren disease, and irregular borders suggest a possible neoplasm. However, sialography is not the preferred imaging technique for identifying salivary cancer.[65] Sialography is also contraindicated in the presence of iodine allergy or acute sialadenitis.

CBCT, a more recent entry into the diagnostic technology arena, can also be combined with sialography but is typically used as a stand-alone technique for identifying ductal or stromal calculi. Diagnostic sensitivity and specificity in defining salivary stones have been determined in at least one study to be equal to or greater than other diagnostic methods (98.85%).[66] The technique has also proven adequate for calculating the diameter of the assessed calculi and has proven reproducible as well.[66]

If there is strong consideration for tumor or there is question regarding the nature of a soft tissue mass within a salivary gland, MRI is suggested. Yousem et al provide an excellent algorithm to help guide decision making in terms of major salivary gland imaging.[67] MRI assessment is also useful for discerning intraglandular from extraglandular abnormality, local extension and invasion, and other malignant features (eg, perineural spread), but it also helps to define possible nodal metastases and/or systemic involvement. MRI is the only imaging technique recommended for assessment of the submandibular gland, as any identified nodule or mass that is observed clinically is likely to represent malignant disease.[65]

One of the major weaknesses of MRI is that it is not particularly good at identifying salivary calculi. However, this deficiency may be overcome by the development of a new visualization technique using susceptibility-weighted imaging (SWI) at 3 Tesla—a strategy that yields images possibly comparable to CT or CBCT.[68] This MRI strategy, if proven reliable, may be an important advancement in diagnosing salivary stones in that it is noninvasive and does not involve ionizing radiation or delivery of a sialogogue.

Additional evidence suggests that the use of MR spectroscopy can be helpful in differentiating benign salivary gland tumors from those that are malignant and for distinguishing between Warthin tumor and pleomorphic adenoma.

Fine-needle aspiration cytology

Another minimally invasive approach for defining potential salivary neoplasm is image-guided fine-needle aspiration cytology (FNAC).[69] The technique involves insertion of a narrow-gauge (25-22 G) needle into the gland to accumulate cellular tissue for microscopic examination.[70] Possible limitations associated with FNAC may include (1) the procedure does not help in defining glandular architecture (2); while the sensitivity, specificity, positive predictive value, and negative predictive value in the detection of benign lesions appear reasonably high (98.52%, 87.05%, 94.36%, and 96.55%, respectively), the value for sensitivity is far less when computed for the detection of malignant lesions (77.77%, 98.78%, 93.33%, and 95.29%, respectively)[69] ; and (3) the technique may not be reliable in defining palatal minor gland abnormality and malignant lesions.[71, 72]

In the study by Ashraf et al (2010),[69] FNAC did not correctly identify 4 lesions as malignant and misdiagnosed one benign lesion. These findings appear consistent with similar studies of the technique when used for assessing potential pathology associated with the submandibular gland (in comparison with histology) (sensitivity and specificity, 71.4% and 94.4%, respectively).[73] Conflicting data have also been published that suggest the sensitivity and specificity of FNAC is higher than that cited above; in one study of 54 benign and 28 malignant lesions involving salivary gland tissue, the sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value were 28 (90%) of 31, 54 (98%) of 55, 82 (95.1%) of 86, 96%, and 94%, respectively.[74]

Also see Fine-Needle Aspiration of Salivary Glands.

Elastography and ultrasonography

Several recent innovations have improved evaluation of the effect of treatment for obstructive salivary disease. These include elastography,[75] which is useful in monitoring potential fibrosis of the gland parenchyma following obstructive disease and sialolithiasis, and contrast-enhanced ultrasonography,[76] which allows analysis of functional vascularization post recurrent sialadenitis due to obstruction.

Sialoendoscopy, a minimally invasive technique[77] like endoscopy, involves insertion of a very small camera into the duct to allow visualization of the internal structure of both the duct and gland. It is recommended for assessment of the effects of sialolithiasis, stenosis, and recurrent swelling, as well as recurrent infection.[47, 78, 79, 80] While generally considered safe, sialoendoscopy is not without risk. It has been reported to cause acute upper airway obstruction

secondary to perforation of the mandibular gland duct, with subsequent salivary extrusion and edema of the tongue.[81]

In a study in which MR sialography was compared with ultrasonographic and videoendoscopic assessment of parotid and submandibular gland stenoses and sialectasia, it was found that MR defined calculi not identified initially by dynamic color Doppler ultrasonography (confirmed by videoendoscopic evaluation). The authors conclude that MR sialography may be a valid method for the evaluation of salivary duct disorders, with the added benefit of being noninvasive.[82]

Dental Intervention

Dental management of Sjögren syndrome and other nonmalignant conditions causing oral dryness consists of saliva replacement therapy, prevention of caries and oral infection (most often candidiasis), and palliative relief. It may also include providing medication to stimulate salivation if this has not previously been prescribed by the patient's physician. Oral dryness can also be relieved by a number of simple self-help strategies, which should be recommended, including discontinuation of caffeine and alcohol consumption, sucking on sugar-free candies, humidifying the bedroom environment, adding water to food, avoiding salty foods, frequent sipping of water, and allowing ice to melt in the mouth. Coating the lips with petroleum jelly (eg, Vaseline) and lip balm (eg, Blistex) may also reduce the perception of oral dryness.

Over-the-counter commercial saliva substitutes, which contain thickening agents such as carboxymethylcellulose or mucin, persist longer than water. These include Moi-Stir, Optimoist, Orex, Sage Moist Plus, Salivart, Ora Lube, Xero-lube, Oral Balance (a gel), and Plax. Chemical stimulants include mouth coat and Optimoist. A comprehensive list of products that stimulate salivary flow and oral moisturizers, special toothpastes, mouthwashes, and other products and devices for cleaning the teeth and tongue, as well as remineralizing and protecting teeth, can be found in *Dry Mouth, The Malevolent Symptom: A Clinical Guide*.[83]

In patients with some salivary function, a number of sugarless gums may also be recommended as stimulants, including Biotene (sweetened with xylitol), Eclipse (sweetened with maltitol, sorbitol, mannitol, aspartame, and acesulfame K), Extra (sweetened with sorbitol, mannitol, maltitol, acesulfame K, and aspartame), Trident (sweetened with sorbitol, mannitol, acesulfame, and aspartame), Xylifresh (sweetened with xylitol), and Salix.

The problem with gum is that in edentulous or partial edentulous patients, the product may stick to the full or partial denture and chewing can also cause abrasions under the appliances.

Two other relatively new products that may also be useful in managing dry mouth (including dry mouth associated with Sjögren syndrome) include Ora Moist Time-Released discs and Xylimelt domes. These discs or domes are placed on and adhere to the oral mucosa and dissolve over time, thus providing a constant taste stimulant. Xylimelt domes can also be used at night, with evidence suggesting the product may effectively reduce the perception of nighttime and subsequent morning dryness.[84]

Sjögren syndrome patients with significant xerostomia may not all respond in the same manner to the prescription of saliva substitutes, so it may be necessary to try a number of different products during management of the problem.[85] . Mucoadhesive polymers (polyacrylic acid) may be a more useful intervention for the patient with extremely low (or no) salivary flow rates, while patients who are able to secrete saliva might benefit from substitutes with moderate mucoadhesive and high elastic properties (eg, in xanthan gum), which stimulate natural gland function to improve moistening and lubrication.[85]

Muscarinic agonist medications (eg, pilocarpine, bethanechol, cevimeline) can help in reducing dryness, but only clinicians knowledgeable in their use and aware of their significant adverse effects should prescribe these drugs. Regardless, the patient's physician of record should be consulted. Adverse effects can include allergic reactions, confusion, irregular heartbeat, stomach upset/pain, sweating and facial erythema, tremor, elevations in blood pressure, fatigue, vomiting, vision changes, and headache.[86, 87]

Nondrug therapies, including acupuncture and electrostimulation strategies, have also been proposed as treatment of dry mouth, but these interventions lack well-controlled clinical trials. One novel approach includes a mandibular appliance that has an integrated battery and electrode that can be activated via remote control to stimulate the submandibular and sublingual glands.[88] In a cross-over, randomized, sham-controlled, double-blinded multicenter study, the subjects who received electrical stimulation for 10 minutes demonstrated a sensor-determined reduction in oral dryness.

Surgical Intervention

The literature with respect to surgical intervention is extensive and provides some interesting glimpses into the latest techniques for managing salivary stones. One such paper reports a prospective study suggesting that sialodochoplasty may be an effective surgical intervention for managing sialolithiasis.[89] Another reported approach to the management of sialolithiasis is the use of the diode laser. A

success rate of 92%, with few complications, was reported in at least one case series involving this surgical intervention.[90] An anecdotal report suggests that submandibular sialoadenectomy using video assistance may also be useful in gland resection,[91] and a case series (3 patients) notes successful treatment of ranula via injection of botulinum toxin type A.[92]

In a larger case series, 323 submandibular and 132 parotid calculi were treated using extracorporeal shock-wave lithotripsy (ECSWL) coupled in some cases with fluoroscopically guided basket retrieval or intraoral stone removal under general anesthesia. Historically, this technique has been used to treat kidney stones and involves the application of an externally applied, focused, high-intensity acoustic pulse. The overall success rate reported for the 3 techniques was 76.5%. However, total success, defined as the complete elimination of the stone and symptoms, occurred in only 39.4% of those patients treated exclusively with the ECSWL.[93]

A good update on the latest surgical techniques and their supporting studies can be found in the article by Gulati and colleagues published in the *British Journal of Maxillofacial Surgery*.[1]

Salivary Constituents as Measures of Health

Constituents in whole saliva can be used to assess a number of systemic diseases, such as chronic kidney disease,[94] various cancers (eg, oral squamous cell carcinoma,[95] breast carcinoma,[96] epithelial ovarian cancer[97]), some hereditary diseases (eg, cystic fibrosis[98]), and congenital adrenal hyperplasia.[99]

Evidence also suggests that saliva constituents may help in the identification and monitoring of a number of infectious diseases such as Lyme disease,[100] lung infection,[101] and viral diseases such as viral hepatitis (A and B).[102] Saliva may also serve as a marker of rotavirus in newborns,[103] dengue infection,[104] and HIV infection.[105] Herpesviruses (eg, herpesvirus 8, cytomegalovirus, Epstein-Barr virus) are also shed in saliva and can be identified via salivary analysis.

Saliva has been extensively studied as a means of drug monitoring (prescribed and illicit).

Endocrine function can be evaluated via salivary whole saliva assessment of cortisol.[106] . Raff provides a good review of the usefulness of cortisol measurements in saliva as a reliable test to evaluate Cushing syndrome and adrenal insufficiency.[107] Raff concludes, based on a systematic review of studies from 1950-2009, there is 90% sensitivity and specificity associated with assessed salivary cortisol in the detection of adrenal insufficiency.

Measurement of cortisol has also been suggested as a means of determining the relative level of stress in pregnant women with blood and injection phobia.[108] In this study, pregnant women with this psychological condition were found to have a higher output of cortisol in comparison with women who were not identified as phobic (P = .014).

The perception of distress in women with temporomandibular disorders has also been evaluated via cortisol levels,[109] although results have been mixed. In Nilsson and Dahlström's study,[110] morning levels were not related to perceived distress, while in the Da Silva et al study using the Research Diagnostic Criteria, females identified as having a temporomandibular disorder demonstrated significantly greater cortisol levels in morning saliva compared with corresponding controls.

A number of salivary constituents have also been used in the assessment of autonomic disorders. For example, salivary alpha-amylase (sAA) (a putative correlate of norepinephrine) and cortisol have been used to evaluate 2 samples of children with autism spectrum disorder.[111] Salivary sAA has also been evaluated as a specific sympathetic marker for dysfunctional autonomic and hypothalamic-pituitary-adrenal axis activity in the assessment of some behavioral disorders.[112, 113]

Treatment of Excessive Salivation

Excessive salivation (sialorrhea) can result from a variety of neurologic disorders (eg, cerebral palsy, mental retardation, Parkinson disease), medication use (eg, lithium, cholinergic agonists), intraoral irritation (eg, from disease such as painful aphthous ulceration), or mandibular surgery (as a consequence of loss of muscular control). It also occurs as a result of rabies and heavy metal poisoning.

Historically, sialorrhea has been managed with anticholinergic medication, such as scopolamine, and surgically via submandibular gland excision or ductal ligation and relocation, or via tympanic neuroectomy with chorda tympani sectioning. Medications that appear to effectively control drooling include scopolamine and benztropine. A reduction of 30-60% has been reported in one study, with the greater decrease relating to the application of 2 transdermal patches of scopolamine.[114]

Other medications

Glycopyrrolate

In 2010, a synthetic anticholinergic that acts on peripheral versus central muscarinic receptors, glycopyrrolate, was approved by the US Food and Drug Administration (FDA) for administration to children aged 3-6 years who have chronic neurologic disorders and severe drooling. In 2011, the drug was introduced to the market and is now available to patients by prescription.

A recent systematic review of studies assessing glycopyrrolate[115] reveals 6 trials that assessed the drug for drooling in children. In one double-blind, cross-over trial of 27 patients aged 4-19 years, the mean drooling score was significantly less when compared with placebo. Another study of 36 subjects aged 3-16 years also demonstrated treatment effectiveness of the drug, which was titrated at 0.02 mg/kg/dose orally taken thrice daily (not to exceed 3 mg) over a 4-week period.

Reported adverse effects for glycopyrrolate include constipation (20.4%), vomiting (17.5%), diarrhea (17.5%), pyrexia (14.6%), dry mouth (10.9%), flushing (10.9%), nasal congestion (10.9%), and behavioral changes[116] ; further, since toxicity appears to increase concurrently with increased dosage, the authors recommend that patients be carefully monitored during use. A solution of 1 mg/5 mL is said, however, to be well tolerated over 24 weeks by pediatric patients aged 3-18 years.

More information about glycopyrrolate oral solution is available from WebMD.

Atropine

Atropine(Sal-Tropine Oral) is another medication that can be used to control excessive salivation and drooling.[117] The calculated dosage (0.4 mg/75 pounds of body weight) is taken by mouth every 4-6 hours as needed.

Anticholinergic drugs should not be taken by patients with history of allergy, eye adhesions, asthma, bowel or stomach blockage or other bowel muscle weakness problems, ulcerative colitis, bleeding, glaucoma, myasthenia gravis, prostate problems, difficulty urinating, excessive stomach acid, or difficulty swallowing. Anticholinergic drugs also may interact with other medications, including the tricyclic antidepressants, antihistamines, and benztropine (for Parkinson disease).

The American Dental Association approved atropine sulfate 0.4-mg tablets as a means of reducing salivation during restorative dental procedures during which moisture control is deemed important. Adults may require 0.6 mg to up to 1 mg to achieve real clinical oral dryness. The dosage for children is 0.01 mg/kg of body weight, not to exceed 0.4 mg in a 4- to 6-hour period.[118]

Additional information on oral atropine can be found through WebMD.

Botulinum toxin

Injection of botulinum toxin has also been studied as a means of reducing drooling in patients with neurologic dysfunction.[119] It has been found to effectively reduce salivation, but the duration of effect appears to vary among individuals. In one study, 7 of 33 drooling patients requested a second injection after 4-7 months. The literature suggests that differences in response exist based on the type of disorder present (eg, cerebral palsy vs operculum syndrome, which involves spastic paralysis of the muscles of mastication, along with other muscle groups of the face and neck).

A 2007 systematic review of the botulinum toxin literature of studies assessing the potential treatment efficacy for sialorrhea revealed 15 studies that included 4 controlled trials. In all of the controlled studies, botulinum toxin A was found to significantly reduce saliva production and improve subjective symptoms. However, as the authors indicate, additional research is necessary to fully define the best dose to be used, the ideal injection location, and the most efficacious technique.[120]

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