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Review Article

Sjögren's Syndrome: A Brief Review to Newly Qualified Dentists

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Introduction

The term "dry mouth" has been used as either a description of an objective finding called salivary hypofunction, or a subjective description of a patient's sensation called xerostomia. [1,2] In the last 20 years, it has been found that the occurrence of xerostomia is about 10% among people over age 50 and 40% for people over age 65.[3] Sicca complaints are very common and require various tests to reach a diagnosis. The most common causes of dry mouth are 1) xerogenic drugs such as antihistamines, antihypertensives, antidepressants, diuretics and antipsychotics; 2) radiotherapy to the head and neck; 3) Sjögren's Syndrome (SS); 4) connective tissue diseases such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and systemic sclerosis; 5) HIV or chronic active hepatitis. [4]

Assessment

History and Examination

Firstly, a thorough history including the chief complaint, dental problems, medical history and medications should be taken. In the presence of SS, extraoral examination may reveal glandular (salivary or lacrimal) enlargement which may exhibit firm, diffuse and non-tender enlargement. Additionally, the patient should be examined for any angular cheilitis as it is a common sign caused by xerostomia [5-7] .Figure 1. Intraoral examination would assess 1) the dryness of the mucous membranes; 2) dry lips; 3) touch sensitivity response to dental instruments; 4) any dental cervical margin caries; 5) absent or cloudy saliva expressible from the parotid or submandibular duct; 6) overgrowth of Candida species producing oral erythema; 7) hyperlobulated tongue with loss of filiform papillae [5,6]. Sublingual salivary pooling can be examined by drying under the tongue and monitoring salivary secretion over a minute. Abundant secretion of saliva is strong evidence against salivary hypofunction [7] Figure 1.

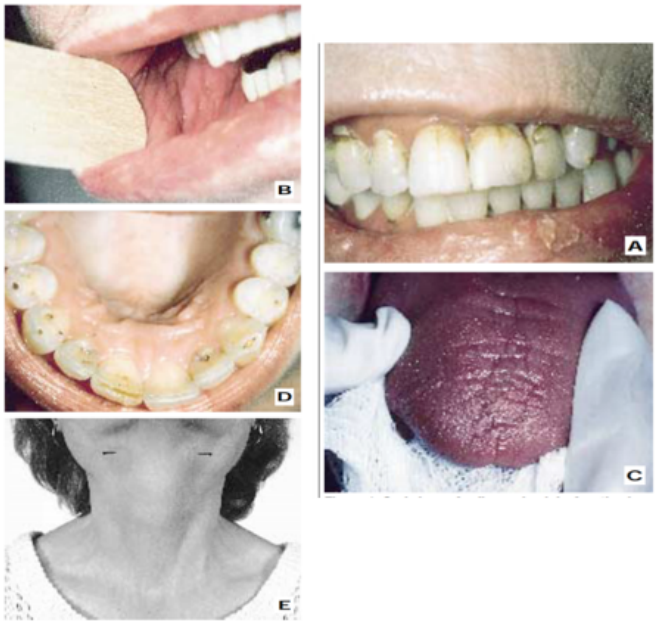

Figure 1: Oral signs of salivary gland dysfunction in Sjögren's syndrome. [8] A. Dryness of the lips and marginal caries B. Dryness of the mucosa intraorally. C. Extreme desiccation of the tongue with depapillation. D. Caries on the cusp tips. E. Chronic enlargement of the major salivary glands (arrows).

Initial eye evaluation is equally as important and should check for any 1) irritation or discomfort which may be described by the patient as burning or stinging sensation; 2) dryness; 3) redness of the conjunctiva; 4) ocular fatigue; 5) photosensitivity. [9] In addition, the patient might be examined for sensory peripheral neuropathy as it is common among patients with SS and is associated with the presence of anti-Ro and anti-La.[10] The patient should be asked about her physical capacity as it

has been found that women with pSS have experienced muscle weakness and fatigue.[11]

Differential Diagnosis

After ruling out all the systemic diseases and medications that could cause sicca symptoms, a provisional diagnosis of SS can be made. SS is a chronic systemic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates of the affected glands and epithelia. [12,13] It is estimated to be the second most common immune disease after Rheumatoid Arthritis (RA) among the group of rheumatic diseases. The estimated prevalence of SS ranges between 0.5% and 1.56%, based on the diagnostic criteria, with a female to male ratio of 9:1. SS is most commonly diagnosed in the age groups 20-30, and after menopause in the mid-50s. [14-17] SS can present alone which is called primary Sjogren syndrome (pSS) or may occur in conjunction with another rheumatic disease such as RA, SLE or progressive systemic sclerosis. In this case it is called secondary Sjogren syndrome (sSS).[14,18,19] Clinical manifestations of SS can vary considerably from mainly xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes) to developing severe systemic complications such as vasculitis, glomerulonephritis, a host of neurological manifestation and 5% of patients may develop lymphoma.[12,13,20] The aetiology of SS is unknown, however there are a few studies suggesting that SS shows class 2 Major Histocompatibility Complex (MHC) genes which is a genetic risk factor for the development of autoimmune diseases and could be involved in SS [21,22].

While others found that Human Leukocytes Antigen (HLA) class 2 markers HLA-A1, -B8, or -DR3/DQ3 haplotypes in white patients are linked to susceptibility to SS [16]. However, it has been found that the relationship between HLA and SS is restricted to patients holding anti-SSA and/or anti-SSB antibodies. [22] Additional studies been published concerning the role of some viruses such as Epstein-Barr virus, Hepatitis C virus, human T-cell leukemia and HIV; however, no single specific virus has been shown to be closely involved. [23,24] The pathophysiology of SS has been extensively studied and it has been found to be multifactorial and thought to involve immunological, hormonal, genetic and viral components. [25] Immunologically, it is found that immune cells, both cytokines and chemokines have an important role systemically and locally in the salivary and lacrimal glands, the main organs for the disease. [26] Patients with pSS have an activated type 1 interferon (INF), which are cytokines interfering with virus infections. It has been suggested that INF contributes to breakdown of tolerance and stimulation of an autoimmune response, however the critical steps of the mechanism behind INF in relation to SS are unknown. Production and action of interferon-α in SS can be seen in Figure 2 [23,27].

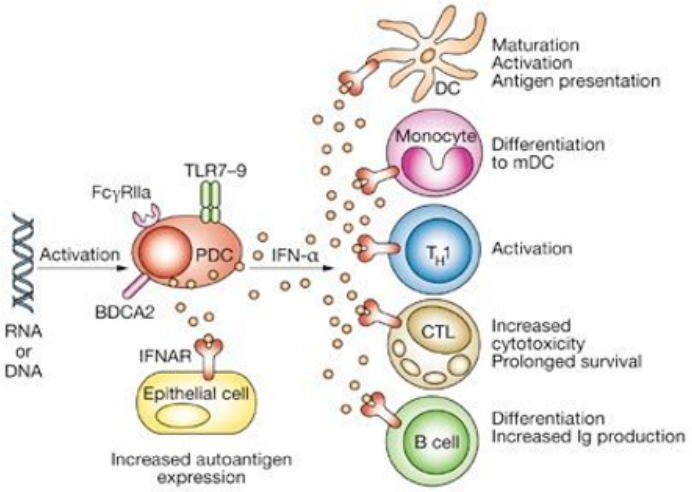

Figure 2: Activated Plasmacytoid Dendritic Cells produce interferon-α that acts on the interferon-α/β receptor. Interferon-α has pleiotropic activating effects on the adaptive immune system and increases the expression of Ro52 autoantigen in salivary gland epithelial cells. [23]

Other studies have shown that anti-Ro- and anti-La-producing B-cells were presented in the lymphocytic infiltrates of the affected glands. It has been thought that those cells are affecting glands' function by: 1) secretion of cytokines; 2) production of auto-antibodies that interfere with muscarinic receptors; 3) secretion of metalloproteinases that interfere the interaction between the glandular cell and extracellular matrix. [28,29] However, some advocate that hormones such as oestrogen may be the main cause of difference in incidence between men and women. It has strong effects on auto-immune diseases and it is essential for initiation of autoimmunity. [30] Oestrogen expressions play a role in specific cellular sensitivity to female hormones. Females produce higher immunoglobulin at base line and in response to infection or immunisation compared to males.[31] Additionally, androgens may protect from autoimmunity and it has been found that women with SS have androgen deficiencies. [32] However, the following conditions could mimic SS because of their potential effect on both lacrimal and salivary gland; Table 1.

Condition	How to be distinguished from SS
Age-related sicca syndrome	Evidence of immune system disease (anti-Ro/SSA and anti-La/SSB) are usually negative in those patients.
IgG4-related disease	By clinical and laboratory features and the distinct histopathologic findings seen in IgG4-RD.
Benign lymphoepithelial sialadenitis and dacryoadenitis	It has the histopathology characteristic of advanced SS, which are islands of epithelial cells within lymphoid infiltrate of the ductal epithelium. Patients can be defined during the evaluation of salivary gland enlargement.
Lymphoma and other hematologic malignancy	Malignant infiltration of the parotid may happen in both children and adults. It presents with bilateral salivary and lacrimal gland enlargement.
Sarcoidosis	Usually it can resemble SS but can be distinguished by biopsy.
Hepatitis C	Despite that clinical and immunologic findings may be similar, some histologic features may differ and symptoms of dryness may be less frequent.
HIV infection	Diffuse CD8 lymphocytosis syndrome is a manifestation of HIV infection. Salivary gland biopsies show a CD8-predominant lymphocytic infiltrate.
Graft-versus-host disease (GvHD)	the extent of lymphocytic infiltration was less than in SS, and patients can generally be distinguished from those with SS based upon the clinical examination.
Systemic vasculitis	Bilateral parotid and submandibular gland enlargement are rare manifestations of granulomatosis with polyangiitis (GPA). Clinical, laboratory, and histologic tests can distinguish GPA from SS.

Table 1: Entities may mimic SS because of their potential involvement of both the lacrimal and salivary glands [7].

Classification Criteria

The diagnosis of SS is usually difficult and requires a multidisciplinary approach, because sicca symptoms are common, non-specific and there is no gold standard diagnostic test. [33] The diagnosis is usually made retrospectively when patients experience more severe complications than sicca such as vasculitis, arthritis, parotitis, etc. [16] However, there is a disagreement among physicians about the diagnostic criteria of SS. As in patients with milder sicca symptoms and less characteristic antibody profiles, diagnosis and therapy are difficult. [14]. Many sets of classification criteria have been proposed in the last fifty years. The 2002 revised American-European Consensus Group (AECG) classification criteria have had widespread acceptance and adoption in clinical application and studies of SS. The AECG criteria consist of six criteria, two subjective and four objective. [33] Table 2.While, in 2012 the American College of Rheumatology (ACR) declared a new set of preliminary criteria proposed by the Sjögren's International Collaborative Clinical Alliance (SICCA). They are focused on three objective features. [34] Table 2. Studies showed that both criteria have a similar performance among patients and there was no clear evidence for increased value of ACR over the AECG from clinical or biological perspectives. [33,35] In 2016, ACR and the European League Against Rheumatism (EULAR) developed and validated an international consensus of data-driven classification criteria for pSS. It has both common characters of ACR and AECG. [16,36,37] It eliminates the performing of salivary gland scintigraphy and parotid sialography. It clarifies the autoantibody role to include only anti-Ro/SSA antibodies and incorporates the new SICCA ocular surface staining scoring scheme, designed for ocular surface examination that use both fluorescein and lissamine green as ocular surface dyes. [7] The ACR/EULAR criteria is based on a weighted scoring system; it applies to any individual who meets the inclusion criteria, exclusion criteria and has a score of ≥4 on the weighted score system. [7,37] Table 3.overlap between five conditions in the exclusion criteria for AECG and ACR/EULAR. These are (past head and neck radiation treatment, Hepatitis C infection, AIDS, sarcoidosis, GvHD). The conditions which differ in the exclusion criteria are pre-existing lymphoma and use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug) in AECG, and Amyloidosis and IgG4-related disease in ACR/EULAR [33,38].

Inclusion Criteria	AECG	ACR
I. Ocular symptoms; At least one positive answer	1- have you had daily or persistent troublesome dry eyes for more than 3 months? 2- do you have recurrent sensation of sand or gravel in the eyes? 3- do you use tear substitutes more than 3 times a day?	None
II. Oral symptoms; At least one positive answer	1- have you had a daily feeling of dry mouth for more than 3 months? 2- have you had recurrently or persistently swollen salivary gland as an adult? 3- do you frequently drink liquids to aid swallowing dry food?	None
III. Ocular signs; objective evidence, a positive result for at least one of the following two tests	1- Schirmer's I test, performed without anaesthesia (≤5 mm in 5 min). 2- Rose Bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)	Keratoconjunctivitis sicca with ocular staining score ≥3 (patient is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)
IV. Histopathology;	Minor salivary gland biopsy showing focal lymphocytic sialadenitis, with a focus score ≥1.	Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2
V. Salivary gland involvement; objective evidence, a positive result for at least one of the following tests	1- Unstimulated whole salivary flow (≤1.5 mL in 15 min). 2- Parotid sialography showing the presence of diffuse sialectasis (punctate, cavitary or destructive pattern), without evidence of obstruction in major ducts. 3- Salivary scintigraphy; showing delayed uptake, reduced concentration and/or delayed excretion of tracer.	None
VI. Autoantibodies; presence in the serum of the following autoantibodies:	Antibodies to Ro (SSA) or La (SSB) antigens, or both	Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titre ≥1:320)
Classification rules	1. Patients without any potentially associated disease are diagnosed with primary SS; A. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item (histopathology) or (serology) is positive. B. The presence of any 3 of the 4 objective criteria items (III, IV, V, VI) C. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey. 2. In patients with a potentially associated disease, the presence of item I or item II plus any 2 from among items III, IV and V may be considered as indicative of secondary SS	Patients who have at least 2 of the 3 objective features previously described would be described with SS. Eliminated the distinction between primary and secondary forms of SS

Table 2: Illustration of AECG and ACR classification criteria [13,16,33,34,36,39].

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm^2	3
Anti-SSA/Ro positive	3
Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least 1 eye	1
Schirmer's test ≤5 mm/5 minutes in at least 1 eye	1
Unstimulated whole saliva flow rate ≤0.1 ml/ minute	1

Table 3: The ACR/EULAR weighted score system [7,37].

Investigations

Patients should be asked the aforementioned screening questions and should undergo the required tests based on the chosen diagnostic criteria:Sialometry; it is the measurement of salivary flow in two ways. First, the collection of whole saliva which is the common method because it is straightforward, requiring only a few minutes, without the need for any special equipment. However, it does not detect any salivary gland dysfunction or gland specific sialochemical changes and only a reduced rate of unstimulated whole saliva is considered as a diagnostic tool for SS. Secondly, the collection of glandular saliva which may reveal hyposecretion of specific salivary glands, and sialochemistry of the collected saliva may show changes in electrolytes and proteins reflecting the autoimmune invasion on the secretory cells. [40,41] Schirmer's I test; it was introduced in 1903 and includes the use of Whatman 41 special strip placed in the lower eyelid. It measures the basal tear secretion with the conjunctival-lacrimal trigeminal reflex.[42] Rose Bengal or other ocular dye score: its ocular surface staining patterns help in defining dry eye and gauge severity. It concentrates in corneal and conjunctival cells that lack a healthy mucin barrier.[43] Minor salivary gland biopsy showing focal lymphocytic sialadenitis: it is the number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue. [33] Figure 3.

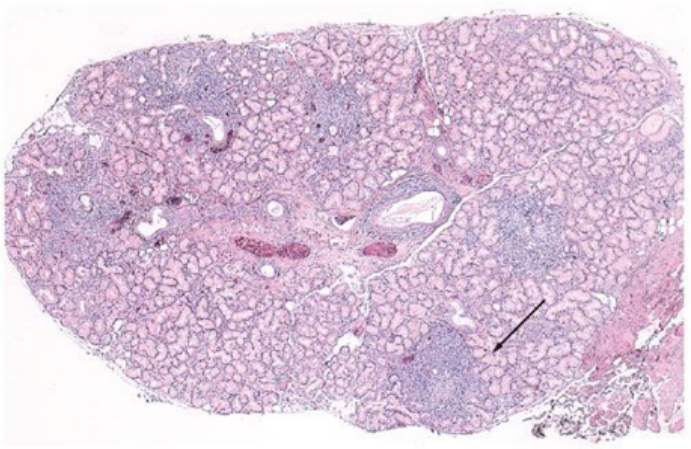

Figure 3: Minor salivary gland biopsy from a patient with SS. Multiple lymphocyte foci are prominent and seen around glandular ducts (arrow) [23].

Management

Treatment of SS is mainly symptomatic and is directed toward controlling sicca complications as early as possible. It focuses on damage resulting from corneal ulcerations and chronic xerostomia. However, currently there are no evidence-based therapeutic guidelines. [18] Therefore, in the last thirty years the treatment of SS was limited to the use of substitute agents for sicca symptoms, glucocorticoids and immunosuppressive agents.[44] The treatment of dry eyes primarily focuses on alleviation of symptoms, which may include replacement therapy, local stimulators of tear secretion and anti-inflammatory agents. [45] Artificial tears would be used alone as first-line therapy. The patient is already using Viscotears which are polyacrylic artificial tears - clear liquid gel with high viscosity. It has longer ocular time retention compared to polyvinylalcohol. That may relieve the symptoms of dry eyes. [46] In severe dry eyes symptoms, topical ciclosporin showed to be efficient in treating various ocular surface disorders particularly dry eyes and severe allergic keratoconjunctivitis.[47] Additionally autologous serum eye drops showed potential advantage over traditional lacrimal substitutes, however studies found that there

was some benefit in the short-term but no evidence of an effect after two weeks of treatment [48].

The treatment of dry mouth is mainly palliative despite that some medications have been shown to be effective. Salivary substitutes and hydration of oral tissue are considered the first-line therapy. [16] There are a wide variety of preparations as saliva substitutes, in the form of gel, sprays or oils, all can improve lubrication and protection from noxious environmental agents. Studies found that oxygenated glycerol triester spray is more effective than electrolyte spray. However, saliva substitutes are not generally accepted by patients as they are short-lived and unappetising, whereas oral moisturising gels last longer and are suitable for bedtime. [18,49] It has been found that chewing gum increased salivary production and may be preferred by patients, however there is no evidence showing that gum is better or worse than saliva substitutes.[49] Regarding non-pharmacological alternatives, there is little evidence to support the effectiveness of electrostimulation devices or acupuncture therapy on dry mouth symptoms. [50] Studies have shown that systemic agents as cholinergic drugs (pilocarpine, cevimeline) which stimulate tear and saliva secretion are effective in relieving sicca symptoms, increasing salivary production and improving subjective and objective parameters. [44,45,51] As well, Omega-3 supplements were seen to help in improving salivary flow and ocular symptoms. [52,53] Clinically it has been found that cholinergic drugs are safe, well tolerated with no serious side effects or drug-to-drug interactions of concern, however it is best to avoid them in patients with respiratory diseases and those who are taking antihypertensives. [54]

However, there is insufficient evidence to determine that other medications such as corticosteroids, methotrexate and rituximab are effective in the treatment of sicca symptoms. [53,55-57] Dental care including frequent regular dental check-ups and office and home fluoride application is essential to prevent any further caries and to detect any oral candidiasis or angular cheilitis. [45,53] The best recommended treatment for fatigue symptoms was found to be exercise and attention to diet, which provide the same benefit seen in patients with RA, SLE or multiple sclerosis. [53]

Monitoring and follow-up

Firstly, a detailed explanation of symptoms of the disease should be given to patients, which may facilitate keeping symptoms under control. Regular follow-up is essential to manage any systemic manifestations/extra glandular complications such as anaemia, renal tubular acidosis and peripheral or autonomic neuropathy and malignant lymphoma [16].

Conclusion

The difficulty of diagnosing SS comes from the fact that patients present with vague symptoms which could attributed to a range of causes. Unfortunately, it can take a long time and several visits to a range of clinicians before the patient is correctly diagnosed. It is important to remember that the oral cavity can reveal many signs about an underlying systemic condition, whereas, dentists may not consider asking patients about any other systemic manifestations and solely focus their history taking on oral problems. Until the precise aetiology is known, management may be limited to symptomatic relief. Monitoring and follow-up is vital in detecting any potential serious complications of SS.

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