SJÖGREN'S SYNDROME – AN UPDATE FOR THE DENTAL PRACITITIONERS

Review Article

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ABSTRACT

A normal flow of saliva is a luxury we enjoy unconsciously throughout our lives, little realizing the distressing effects that one experiences when this mechanism fails due to different reasons.There are different pathological conditions that cause xerostomia. E.g., salivary gland aplasia, Sjogren's syndrome, chemotherapy, head and neck radiotherapy, Alzheimer's disease, etc. Sjogren's Syndrome (SS) is progressive, debilitating disorder in which the body's immune system destroys the mucinous secretions of exocrine tissues resulting in the hallmark features of dry mouth (xerostomia) and dry eyes (sicca syndrome).

Sjogren's syndrome is of particular interest to the dental profession, since the mouth is a major site of involvement? For optimal oral care of patients with SS, it is essential that the dentist recognize this condition and be involved intimately in the health care delivery team. This is a review on the Sjogren's Syndrome for the same

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INTRODUCTION:

Salivary gland secretions are essential for maintaining the health and integrity of the oral surfaces. The resting flow rate of whole saliva is 0.2 – 0.4ml/min and stimulated flow rate is 1.0 – 2.0 ml/min.[1] Reduced salivary secretion (stimulated and unstimulated) below 0.2ml/min is termed as xerostomia.[2] Sjogren's Syndrome (SS) is a progressive, debilitating disorder in which the body's immune system destroys the mucinous secretions of exocrine tissues resulting in the hallmark features of dry mouth (xerostomia) and dry eyes (sicca syndrome)[1] (Figure 1)

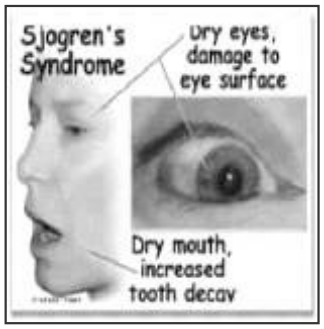

FIG 1: Sjogren's Syndrome

Reduced salivary flow is of importance to the dental profession as there is subsequent loss of the antibacterial properties of saliva, which accelerate infection and aggravate different oral conditions like tooth decay and periodontal disease.[2,3] For optimal care of patients with SS, it is essential that the dentist recognize this condition and be involved intimately in the health care delivery team. This article reviews the Sjogren's Syndrome and its oral implications.

HISTORY AND EPIDEMIOLOGY

The history of this disease is chronicled in a 1987 book entitled *Sjogren's Syndrome: Clinical and Immunological Aspects*.[4] The first description of SS is generally credited to Johann Mikulicz in 1892.[5] However, the disease is named after a Swedish ophthalmologist Henrik Samuel Conrad Sjogren who studied the disease and published his findings in 1933 in his doctoral thesis. Over the next decades, many papers described the disease, and it appeared that rheumatoid arthritis was related to this syndrome.[4,6]

A recent review of surveys by the Centre for Disease Control (CDC) has estimated the prevalence of Sjögren's syndrome in the western countries to be upto 1%[7]; however it was estimated to be 0.5% in North India.[8] It has been reviewed that, Sjogren syndrome is undiagnosed in nearly half of patients, due to its insidious nature.[9]

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ETIOPATHOGENESIS AND CLINICAL FEATURES

Sjogren's syndrome may occur in two forms: Primary Sjogren's syndrome (PSS) and Secondary Sjogren's syndrome (SSS). Primary Sjogren's syndrome manifests only as dry eyes and dry mouth. Secondary Sjogren's Syndrome (SSS) comprises of dry eyes, dry mouth together with a connective tissue or autoimmune disease.[10]

Also, despite extensive study of the underlying cause of Sjögren's syndrome, the pathogenesis remains obscure. In broad terms, the pathogenesis is multifactorial; environmental factors are thought to trigger inflammation in individuals with a genetic predisposition to the disorder. (Figture - 2).

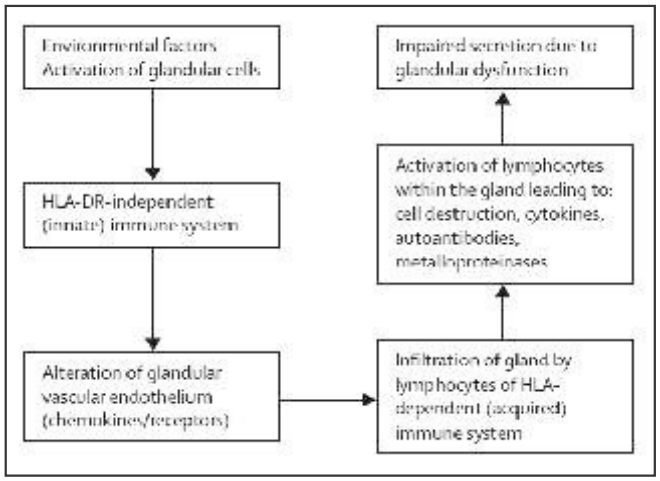

FIG 2 : Etiopathogenesis Of Sjogren's Syndrome

In contrast to many other organ-specific autoimmune disorders, affected tissue can be obtained easily in Sjögren's syndrome by minorsalivarygland biopsy.[9] It has been reported that there are drastic changes in immune homeostasis in the salivary glands before SS patients present to a physician with symptoms of dry eyes and dry mouth.[11] Several theories have been suggested in the pathogenesis of SS, like abnormalities related to the upregulation of type I interferon regulated genes, abnormal expression of B-cell-activating factor (BAFF), environmental triggers like viral infections (HTLV-1, EBV, HIV),[12] activation of HLA independent immune system,[13] autoantibodies - Ro/SSA and La/SSB,[14] autoantibodies to muscuranic M3 receptors, X chromosome linked factors,[15] and hormonal influences (estrogen and prolactin).[16] Oral, ocular and extraglandular manifestations occur as a result of lymphocytic infiltration into other tissues or generation of pathogenetic autoantibodies.[10]

ORAL MANIFESTATIONS

The salivary gland dysfunction in PSS is of significant clinical importance and may cause salivary glande enlargement chronic oral discomfort as well as compromised oro-pharyngeal functions.[17] (Figure - 3)

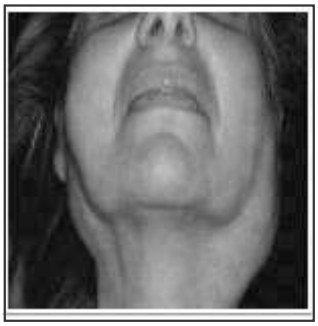

FIG 3 : bilateral salivary gland enlargement

The most common direct consequence of salivary gland dysfunction in Sjogren's syndrome is dry mouth.[18] (Figure - 4)

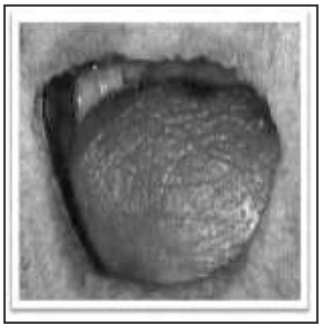

FIG 4: Dry Mouth

Since the extent of salivary dysfunction is variable and patients differ in their tolerance of dryness, symptoms of dry mouth are also variable. SS patients with hyposalivation display a decrease in the concentration of mucin, MUC5B and amylase in the saliva.[19] The mucosa becomes dessicated and friable causing dysphagia, adherence of food to the

buccal or palatal surfaces, trauma while chewing, difficulty in speaking continuously, frequent need to sip water, discomfort with denture wearing, burning sensation on eating spicy food.[2,18]

Numerous signs of reduced salivation associated with Sjogren's syndrome include loss of papillae and a lack of normal salivary pooling beneath the tongue. The tongue may be furrowed, atrophic, coated and/or depapillated.[20] In severe cases fissures may develop on the tongue and lips. The dryness extends to the nose, pharynx, larynx, and nasal sinuses.[21]

Hyposalivation also means fewer buffering and flushing opportunities for the oral hard tissues.[22] Lack of saliva may predispose to atypical dental decay observed on the cervical, incisal and radicular portions of the teeth.[23] (Figure - 5)

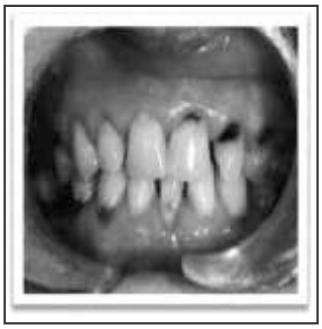

FIG 5 : Cerival Caries

With reduced saliva in the oral cavity, the ability to control opportunistic infections is also reduced.[24] It has been suggested that most PSS patients exhibit oral candidiasis with the clinical appearance ranging from psuedomembranous (white plaques that can be rubbed off) to erythematosus, hyperplastic and angular chelitis.[17]

OCULAR AND EXTRAGLANDULAR MANIFESTATIONS

SS patients present with reduced lacrimal secretions, diminished tear film quality, conjunctival inflammation and corneal ulcerations.[25,26] Ocular complaints may include photosensitivity, erythema, eye fatigue and discharge from the eyes.[3] Secondary form of SS present with a myriad complications like fibromylagia, leucopenia, dry skin, Raynaud's phenomenon, lymphoid interstitial pneumonitis, B cell lymphoma of the mucosa-associated lymphoid tissue (MALT), gasterointestinal disturbances, neurological complications, hypothyroidism, vaginal dryness, glomerulonephritis, etc.[10]

DIFFERENTIAL DIAGNOSIS, DIAGNOSTIC CRITERIA AND INVESTIGATIONS

When approaching a patient with possible SS, it is important to rule out other causes of dry eyes (Xeropthalmia), dry mouth (Xerostomia), parotid gland enlargement and other autoimmune disorders.[3] The differential diagnosis of dry mouth should include Sjögren's syndrome, drug-induced hyposalivation, previous head and neck radiotherapy, pre-existing lymphoma, sarcoidosis, hepatitis C infection, AIDS and graft versus host disease.[27] Early diagnosis and treatment are important for preventing disease complications. The sign of dryness like dry mouth, and caries are very useful signs to start investigating for Sjögren's syndrome.[28] (Figure - 6)

INVESTIGATIONS FOR SJOGRENS SYNDROME
- Ocluar test
  - Schirmer test
  - Slit lamp illumination test
  - Tear break up time test
  - Laser scanning confocal microscopy
- Oral tests
  - Salivary tests
    - Sialometry
    - Sialochemistry
  - Salivary glands tests
    - Biopsy
    - Sialography
    - Scintigraphy
  - Serological tests
  - advanced tests
    - Magnetic resonance imaging
    - ultrasound

FIG 6 : List Of Investigations Of Sjogren's Syndrome

Until recently there were a various set of criteria given for diagnoses of SS.[10] But the discrepancies in the diagnostic criteria led to substantial confusion in

research and clinical trials.[10] Hence, the Sjögren's International Collaborative Clinical Alliance (SICCA) in 2012, proposed a new expert consensus approach consisting of classification criteria based entirely on objective measures. According to this criteria case definition requires at least 2 out of the following 3:[29]

1. Positive serum anti-SSA &/or anti-SSB or [positive rheumatoid factor & ANA ≥1:320]
2. Ocular staining score ≥3
3. Presence of focal lymphocytic sialadenitis with focus score ≥ 1 focus/4mm2 in labial salivary gland biopsies

ORAL TESTS

SIALOMETRY

Sialometry aims to measure the salivary flow, and can be conducted with whole saliva or saliva obtained from a specific gland, both with or without stimulation. For a diagnosis of hyposalivation, the unstimulated whole saliva flow rate (UWSFR) has been proposed as the test of choice, as it may be reduced, even if the stimulated whole saliva is unaffected[30].Values lower than 0.1 ml/min are considered abnormal.[30] This test quantifies salivary secretion from all the salivary glands and is believed to show alterations at the early stages of the disease, being highly reproducible.

According to the Revised International Classification Criteria, the unstimulated whole saliva produced over a period of 15 minutes, without the subjects having eaten or smoked for at least 2 hours, should be measured. A result of lower than 1.5 ml values would transpose to a positive test result for xerostomia.[8] Collection of the stimulated parotid saliva, and subsequent assessment of the flow rate, can be conducted with the help of special suction cups placed over the Stensen's duct. Stimulated saliva is usually collected for 3 minutes and values less than 0.5 ml/min are considered abnormal.[2] Despite the high sensitivity, the stimulated parotid saliva sialometry may fail to reveal alterations at the initial stages of the disease, requires special equipment and may not be easily tolerated by patients.[31] Stimulated saliva assessment can be complicated in patients who do not tolerate the stimulus of salivation and, moreover, due to the wide variety of stimuli used like citric acid, gum, paraffin etc., there is a generalized lack of agreement for normal values.[32]

SIALOCHEMISTRY

Sialochemistry involves the analysis of salivary composition, including both organic and inorganic constituents, by means of different biochemical, electrophoretic and immunological analytical methods. They aim to address the injuries submitted to salivary glands regarding secretion content.[2] Differences regarding protein expression were found between SS patients and healthy subjects. However, individual analysis of SS patients exhibited distinct patterns of protein expression and did not correlate with the clinical, serological or histological severity of disease.[2] Also ionic changes were observed in SS-affected individuals, namely regarding the levels of chloride, potassium, calcium, sodium and magnesium.[17] Furthermore, some SS patients produce little or no saliva which limits sialochemistry applications.[33]

MINOR SALIVARY GLAND BIOPSY

Minor salivary gland biopsy remains a highly used diagnostic procedure for the salivary component of SS.[26,29] (Figure - 7)

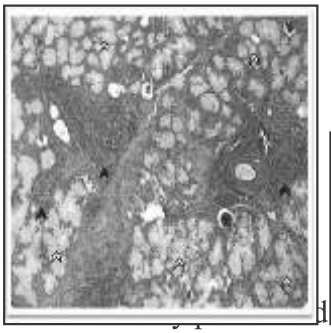

FIG 7 : Labial Salivary Gland Biopsy Showing Multiple Lymphocytic Foci (Black Arrow) And Intact Acinar Units (White Arrow) (Hematoxylin And Eosin Stain, Original Magnification ×100)

l on the internal surface of the lower lip on normalappearing mucosa under local anaesthesia.[30] The biopsy contributes towards the diagnosis of SS if the histopathological examination reveals a mononuclear infiltration with

periductal or perivascular distribution. The inflammatory infiltrate is quantified and a cluster of 50 lymphocytes is termed a focus. The numbers of foci in an area of 4 mm² of tissue surface render the focus score.[2, 30] A focus score of 1or more, as according to SICCA is considered positive for SS diagnosis.[26,28]

A false negative biopsy result range from around 20 to 40% and false positive biopsy results have been found up to 10% of healthy individuals. Patients affected by myasthenia gravis, sialolithiasis and other autoimmune disorders not associated with sicca symptoms may also reveal minor salivary gland infiltration.[32] The extent of infiltrates in a lip biopsy using the same methodological approach may vary greatly from gland to gland in a single patient.

SIALOGRAPHY

This technique requires the radiographic imaging of a salivary gland, following the retrograde injection of a contrast medium through the excretory duct. (Figure - 8)

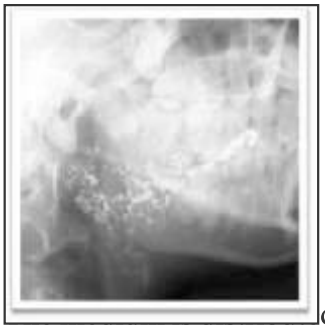

FIG 8 : Sialographic appearance of Sjogren's syndrome (cherry blossom appearance)

d through the duct system, allowing the analysis of the architecture and configuration of the glandular ducts' organization.[2] In SS-affected patients it appears as a dilatation and twisting of the ducts, with an uneven distribution of the contrast medium.[34] Diagnosis is generally based on the classification of Rubin and Holt[35] in which stage 0 (normal) corresponds to no contrast media collection; stage 1 (punctate) refers to contrast media collection = 1 mm in diameter; stage 2 (globular) refers to contrast media collection between 1 and 2 mm in diameter; stage 3 (cavitary) refers to contrast media collection of 2 mm in diameter; and stage 4 (destructive) refers to the complete destruction of the gland parenchyma.

Sialography is a technically challenging, time consuming, painful and risky technique. In fact, it is contraindicated in severe gland dysfunction due to the risk of indefinitely retaining the contrast medium.[34] Also, several reports showed that that the diagnostic value of parotid sialography for diagnosing SS greatly depends on the skills of the observer.[32] Nonetheless, given the potentially high sensitivity and specificity in SS diagnosing, as well as its useful staging potential, sialography still has its use in the evaluation of the oral component of SS.

SCINTIGRAPHY

The oral component of Sjogren's syndrome also may be evaluated by salivary gland scintigraphy. Scintigraphy is a non-invasive method to evaluate the function of salivary glands by observing the uptake and secretion of a radioactive labelled substance (sodium pertechnate of 99mTc).[34] The radionuclide is infused intravenously, and the images of the salivary glands are captured after 1 hour. The uptake of the radionuclide by the glands is observed as well as the amount of saliva containing the radionuclide.[2] InSjögren's syndrome, lower concentration and less secretion into the mouth are seen. The test reports a high sensitivity but a low specificity in SS diagnosis. Also, this technique needs special equipment and staff that can only be found in reference clinical centers. Further, it may be unacceptable for the patient due to risk of radiation damage and high cost.[32]

TREATMENT & PROGNOSIS

As mentioned previously, Sjogren's syndrome (SS) is not only a disease of the exocrine glands but a systemic condition. Therefore, it is recommended that all SS patients should be assessed at appropriate specialist services, which should include oral medicine/dental and maxillofacial radiology, ophthalmology and rheumatology.[27] At present,

only symptomatic treatment is available and no treatment can modify the evolution of SS.[11]

- The primary therapeutic approach to sicca manifestations in Sjögren's syndrome (SS) should be symptomatic relief, using artificial tears and saliva substitutes
- Patients with severe or refractory keratoconjunctivitis sicca might require the addition of topical cyclosporine A to suppress the underlying inflammation
- The treatment of choice for patients with moderate or severe oral dryness and residual salivary gland function is an oral muscarinic agonist
- The management of extraglandular features must be tailored to the specific organ involved, mainly using corticosteroids and immunosuppressive agents.[37] (Table - 1)

DISEASE MANIFESTATIONS & THERAPY (Table - 1)

Manifestations	Therapy
Ocular	
Xeropthalmia Blepharitis Iritis/Uvitis	Artificial tears: preserved/non-preserved Punctal occlusion Topical cyclosporin Topical androgen (in trial) Topical purinogenic receptor agonist (in trial) Topical (non-preserved) steroids Autologous serum tears Lid scrubs for blepharitis Bandage contact lens
Oral	
Xerostomia Periodontitis Gingivitis Oral candidiasis	Mechanical stimulation Regular oral hygiene Topical fluoride Artificial saliva and lubricants Secretagogues, including pilocarpine, cevimeline Anhydrous maltose lozenge Interferon alfa (in trial) Therapy for oral candidiasis Diet modification Gene therapies (preclinical)
Joint/ Muscle	
Arthralgia/myalgia Arthritis/Myositis	NSAIDs Antimalarial drugs Disease-modifying anti-arthritic drugs, including methotrexate, azathioprine, leflunomide TNF inhibitors Anti-CD20 (in trial)
Cutaneous	
Raynaud's syndrome Hyperglobulinaemiapurpura Mixed cryoglobulinemia Erythema multiforme Erythema annulare Necrotising vasculitis Vitiligo, xerosis, alopecia Amyloid anetoderma Embolic and thrombotic lesions	Corticosteroids (topical and systemic) Tacrolimus (topical) Antimalarials Disease-modifying anti-arthritic drugs for vasculitis Cytotoxic agents

Sjogren's syndrome is a disease of exocrine glands which also manifests in other organs.[27] It may plateau or worsen, but very rarely undergoes into remissions. Some people may experience only the mild symptoms of dry eyes and mouth, while others have more severe symptoms of disease.[38] Patients with severe cases are much more likely to develop lymphomas than patients with mild or moderate cases. The most common lymphomas are salivary extranodal marginal zone B-cell lymphomas (MALT lymphomas in the salivary glands) and diffuse large B-cell lymphoma.[39]

CONCLUSION

Sjogren's syndrome (SS) is a slowly progressing autoimmune disease, affecting predominantly middle-aged women, with a female to male ratio reaching 9:1. It is characterized by lymphocytic infiltration of the exocrine glands, mainly the lacrimal and salivary glands, resulting in reduced secretory functions.

The diagnosis and treatment of this disease are frequently delayed, due to the unclear etiology, pathogenesis and multiple system involvement. Dental practitioners can play a crucial role in the early diagnosis and management of the oral manifestations of patients with SS.

Hence, educating the dental practitioners to recognize the disease and refer to the proper specialist should be an ongoing effort.

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