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Sjögren's Syndrome and its oral manifestations –A Review.

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Abstract:

Sjögren's Syndrome is an autoimmune rheumatic disease which is characterized by focal mononuclear cell infiltration of the salivary and lacrimal glands. It typically begins in the fourth to sixth decade of life and the majority [90%] of sufferers are middle-aged menopausal females. The prevalence ratio of women to men is 9:1. Sjögren's syndrome is sub-classified into primary Sjögren's syndrome, consisting of dryness of the mouth (xerostomia) and eyes (keratoconjunctivitis sicca), while secondary Sjögren's syndrome, is associated with other systemic autoimmune rheumatic diseases, such as rheumatoid arthritis, lupus or scleroderma.Since both primary and secondary Sjögren's syndrome share the same signs and symptoms, therefore, they are treated similarly.

Various Oral manifestation include Dental erosion ,Dental caries ,Mucosal friability, Dry cracked or peeling lips ,Angular cheilitis ,Dry plaque laden coarse tongue ,Erythematous tongue ,Fissured tongue ,De-papilated tongue ,Mucositis and Ulcers.

Keywords: Sjögren's Syndrome, oral manifestations, rheumatic disease, salivary gland, lacrimal gland.

1. INTRODUCTION:

Sjögren's Syndrome is an autoimmune rheumatic disease which is characterized by focal mononuclear cell infiltration of the salivary and lacrimal glands. (1). It typically begins in the fourth to sixth decade of life and the majority [90%] of sufferers are middle-aged menopausal females. The prevalence ratio of women to men is 9:1.(2) Sjögren's syndrome is sub-classified into primary Sjögren's syndrome, consisting of dryness of the mouth (xerostomia) and eyes (keratoconjunctivitis sicca), while secondary Sjögren's syndrome, is associated with other systemic autoimmune rheumatic diseases, such as rheumatoid arthritis, lupus or scleroderma.(3) Since both primary and secondary Sjögren's syndrome share the same signs and symptoms, therefore, they are treated similarly.

The most common and earliest symptoms of Sjögren's syndrome are oral and ocular dryness. Oral dryness also known as xerostomia leads to difficulty in talking, tasting, and chewing properly. The most common oral signs and symptoms include tooth decay, fungal infections, traumatic oral lesions, dysphagia, dysgeusia, and inflammation of salivary glands (4). The resulting xerostomia also increases the development of dental plaque and the likelihood of dental caries and periodontal disease (5). Also there is a higher incidence of decayed, missing and filled teeth; and a higher plaque index, gingival index and papillary bleeding index when patients with and without Sjögren's syndrome are compared (6).

Dental professionals are generally the first practitioners to detect Sjögren's syndrome. Since patients suffer from xerostomia, there is impaired saliva production. Saliva helps in swallowing, oral cleansing, speech, digestion and taste. Hyposalivation or chronic xerostomia can also impair the patients' quality of life. Early diagnosis and treatment is very important for preventing complications. Intervention and treatment are of utmost significance. Treatment is generally of palliative and supportive type. Such patients are generally treated with immunomodulators (e.g., hydroxychloroquine, methotrexate) and sometimes with immunosuppressive drugs, reducing and changing the patient's immune response. (7) A thorough understanding of Sjögren's syndrome and its management is essential to help and treat patients. (8)

The objective of this literature review is to summarize Sjögren's syndrome and various oral manifestations along with their management and treatment options.

2. Etiology and Pathogenesis: (9-12)

Although the etiology of Sjögren's syndrome is unknown, multiple factors are thought to be involved in its development. The pathophysiology of Sjögren's syndrome is considered to be continuous stimulation of the autoimmune system. Both B and T cells are considered to be implicated in the pathogenesis of Sjögren's syndrome, even though the mechanisms underlying humoral and cellular abnormalities are unknown.

2.1 Environment: infection by Epstein-Barr virus and Helicobacter pylori bacteria are considered as a possible factor for initiation of Sjögren's syndrome.

2.2 Sex hormones: the majority of Sjögren's syndrome sufferers are females, suggesting that sex hormones may play a role in the autoimmune response. Also androgen deficiency, both locally and systemically, has been pointed out as a key factor. Reduced plasmatic levels (up to 40 - 50%) of de- hydroepiandrosterone sulfate, the precursor sex steroid hormone produced in the adrenal cortex, has been identified in Sjögren's syndrome -affected individuals, when compared to age and sex matched controls.

2.3 Genetics: genetic factors are considered likely to play a role. A genetic predisposition to Sjögren's syndrome has been reported because of multiple reports of two or more members of the same family developing the syndrome. Affected individuals of different ethnic origins however carry different human leucocyte antigen susceptibilities.

2.4 Inflammatory reactivity: the result of an external response can also stimulate inflammation. Lymphocytes generally accumulate in the salivary glands and produce several pro-inflammatory cytokines, therefore sustaining

the disease. An accumulation of lymphocytes, also known as a focus of inflammation, is characteristic in exocrine glands of people with Sjögren's syndrome.

3. Clinical features:

3.1 Ocular involvement: Decreased tear production due to lacrimal gland involvement leads to the dryness and destruction of both corneal and bulbar conjunctival epithelium causing keratoconjunctivitis sicca (KCS). (13)

Symptoms of dry eye may include sensations of itching, grittiness, or soreness, even though the eyes appear normal. Other complaints include photosensitivity, erythema, eye fatigue, decreased visual acuity, discharge from the eyes, and sensation of a film across the visual field. (14)

In more severe cases, functional disability is accompanied with visual impairment.

3.2 Oral involvement: It is suggests that 88% of Sjögren's syndrome subjects had a reduced salivary flow rate, followed by complaints of xerostomia in the 75 to 92% range. (15) Patients with Sjögren's syndrome also suffer from a range of major salivary gland involvement, mainly parotid enlargement, but may sometimes also have isolated submandibular gland enlargement. (16)

Other oral manifestations that are encountered are mainly due to the hypofunction of salivary glands resulting in decreased salivary secretion. So there is loss of the lubricating, buffering and antimicrobial properties of saliva which lends to the incidence of the following conditions: (17-20)

- Dental erosion ,
- Dental caries ,
- Mucosal friability ,
- Dry cracked or peeling lips ,
- Angular cheilitis ,
- Dry plaque laden coarse tongue ,
- Erythematous tongue ,
- Fissured tongue ,
- De-papilated tongue ,
- Mucositis ,
- Ulcers ,
- Oral candidiasis ,
- Halitosis ,
- Oral/dental infection ,
- Impaired taste, chewing, swallowing, and speaking .

4. Diagnosis:

The diagnosis of Sjögren's syndrome is not straightforward as many of the symptoms are subjective and are mostly dismissed initially as other conditions or as an effect of medications. Minor salivary gland biopsy has been traditionally considered as “the gold standard” for the diagnosis of Sjögren's syndrome. (21)

It is very important to recognize SS at an early stage to prevent complications such as dental caries, corneal ulceration, chronic oral infection, and sialadenitis, and also the development of serious extra- glandular systemic manifestations.

5. Diagnostic tests:

5.1 Oral diagnostic tests

5.1.1. Sialometry

Patients with Sjögren's syndrome have a reduced flow rate. Measuring submandibular/sublingual flow rates contributes to an early diagnosis of Sjögren's syndrome. Also, parotid flow rates are considerably decreased in Sjögren's syndrome and Non- Sjögren's syndrome sicca patients. (22) The test should therefore be standardized; the unstimulated whole saliva collection test is performed for 15 min, and the test is considered positive when <1.5 ml whole saliva is collected. (12)

5.1.2 Sialography

Normally fine arborization is seen in parotid ducts, but in patients with Sjögren's syndrome, sialography typically shows sialectasias. (22)

The staging for the sialography can be done as follows:

Stages	Diagnostic information
Stage 0 (normal)	corresponds to no contrast media collection
Stage 1 (punctate)	contrast media collection ≤1 mm in diameter
Stage 2 (globular)	contrast media collection between 1 and 2 mm in diameter
Stage 3 (cavitary)	contrast media collection ≥2 mm in diameter
Stage 4 (destructive)	complete destruction of the gland parenchyma

5.1.3 Scintigraphy

In the scintigraphy test, 99mTc-pertechnate is given intravenously. The typical finding seen in Sjögren's syndrome patients is the decreased uptake in response to stimulation of the parotid and submandibular salivary glands. This test is a sensitive and valid method to measure abnormalities in salivary gland function. (23)

5.1.4 Sialochemistry

Sjögren's syndrome is a mixture of increased inflammatory proteins and decreased acinar proteins as compared to the healthy controls. (24) Furthermore ionic changes were observed in the levels of chloride, potassium, calcium, sodium and magnesium.

5.1.5 Magnetic Resonance and ultrasonography

MR imaging and Ultrasonography are noninvasive techniques that allow the imaging of salivary glands in their physiological state without any artefacts caused by intraductal contrast media or biopsy procedures. MRI is considered a reliable imaging procedure to evaluate glandular alterations. It allows multiplanar evaluation and also processes a high contrast tissue resolution. Characteristically, in Sjögren's syndrome, MRI reveals an internal pattern on both T1 and T2 sequences, with multiple hypo- and hyperintense nodules of different sizes. (24,25)

5.1.6 Serological tests

Serological tests are used to establish the presence of anti-SS-A/Ro and anti-SS-B/La auto antibodies, antinuclear

antigen and rheumatoid factor, based on (enzyme-linked immunosorbent assay). Anti-SS-A/Ro antibodies can also be detected in other autoimmune processes such as rheumatoid arthritis and systemic lupus erythematosus; and so, anti-SS-B/La antibodies are considered to be more specific of SS. Anti- SS-A/Ro can be isolated in 25-65% of cases, and anti- SS-B/La in 13-48%. (26)

6. Others tests include; (27)

6.1 Schirmer's test:

This test is performed for the diagnosis of dry eyes. It assesses tear formation. The test involves placing a filter paper in the lower conjunctival sac of the eyes. If less than 5 mm of paper is wetted in 5 minutes then the Schimer's test is positive for Sjögren's syndrome.

6.2 Lip biopsy:

This involves performing biopsy of minor salivary glands in the lower lip. Lip biopsy report is considered positive for Sjögren's syndrome when there is presence of a focal score of one or more.

A positive biopsy is defined if there is at least one focus of dense, inflammatory infiltrate containing at least 50 lymphocytes/4 mm^2. The lip biopsy may be useful in ambiguous cases or when therapy beyond symptom management is being considered. (28)

7. Extra glandular involvement:

Sjögren's syndrome generally has mucoskeletal, pulmonary, renal, gastroenterological, neurologic, hematologic, thyroid and cardiac involvement. (29)

8. Management:

Management should include local and systemic stimulation of salivary glands, palliative treatment for symptomatic relief, as well as preventing and treating oral complications. (30)

Treatment for most patients is essentially symptomatic. The patient should be asked to regularly visit a rheumatologist as well as an ophthalmologist and a dentist in order to prevent and treat the consequences of mucosal dryness, in addition to extra- glandular manifestations and other associated complications.

8.1 Topical and systemic management

8.1.1 Xerophthalmia: Since xerophthalimia involves dryness of eyes and ulceration Artificial tears & ointments can be prescribed.

- Hydroxyethyl cellulose
- White petrolatum
- Polyvinyl alcohol
- Polyethylene glycol
- Hydroxypropyl methylcellulose
- Methylcellulose
- Carboxymethylcellulose
- Soft contact lenses

Also 'Punctal occlusion' by using a variety of 'plugs' to occlude the punctal openings at the inner aspects of the eyelids can be carries out.

Various medications like Muscarinic agonists: Pilocarpine - Oral pilocarpine, at a dosage of 5 mg twice daily and Cevimeline - Dosage of 30 mg three times daily And Anti-inflammatory medications and Steroids can also be prescribed in severe cases.

8.1.2 Xerostomia:

A. Local Stimulation

The combination of acidic food and chewing , provided by chewing gums or solid food or citric fruits can be very effective in stimulating salivary flow for patients who have decreased salivary function.

The use of laser infrared light of 904nm on salivary glands in the treatment of xerostomia has proved not only to be stimulative but also regenerative (31). Electrical stimulationcan also be used.

Device that deliver a very low voltage electrical charge to the tongue and palate have been described in various literature, although its effect was modest in patients (32).

B. Systemic Stimulation (33)

An agent that has the ability to influence salivary glands to increase the production of saliva is termed as a secretagogue. The four common sialagogues that are extensively used include bromhexine, anetholetrithione, pilocarpine hydrochloride (HCl), and cevimeline HCl.

Pilocarpine is a potent and naturally occurring nonspecific cholinergic agonist which stimulates muscarinic receptors leading to the secretion of water and electrolytes. Initial dose of pilocarpine should be administered 30 minutes before meals, in 5 mg tablets 3 to 4 times a day, with the usual dose range being approximately 3 to 6 tablets a day.

Cevimeline is another parasympathomimetic agonist which is prescribed for the treatment of oral dryness in patients with Sjögren's syndrome and the recommended dosage being 30 mg, 3 times a day. It is capable of inducing salivation with minimal adverse effects.

C. Symptomatic treatment

Palliative treatment remains as only choice in cases when there is no functionally salivary tissue present as is in the disorders of irreversible damage of salivary secretory cells. A number of saliva substitutes have been developed for the palliative care of patients with xerostomia, these agents are available in liquid, spray, or gel forms and have moistening and lubricating properties, also their purpose is to provide prolonged wetness to the oral mucosa.

Salivary substitute generally tend to be short acting and provide relief only for a limited period of time. They are most effective when applied before sleeping or speaking.

Patients affected with xerostomia should also increase their fluid intake. These patients' should be encouraged to place ice chips in their mouth and sip water throughout the day to provide adequate moisture and relief to the dry mouth symptoms (33) .

Acupuncture has also been reported to increase parasympathetic activity, causing a release in neuropeptide, stimulating salivary flow and secretions. Three points are treat-

ed in each ear, and one in the radial aspect of each index finger

Future treatment for some of the salivary gland disorders may require the use of gene therapy and tissue engineering, but at present there is a need to have a greater understanding of the causes and pathogenesis of salivary gland disease before specific therapies can be developed.

8.1.3 Systemic management:

Since SS is an autoimmune disorder; Corticosteroids 6-7 mg/kg/day, Prednisone 1-2 mg/kg/day And Nonsteroidal anti-inflammatory drugs can be prescribed.

Also Immune regulators and Immune suppressors can be prescribed.

Also Natural human interferon alpha can be prescribed 150 IU 3 times daily for 12 weeks

In cases where patient suffers from oral candidiasis, Nystatin tablets or solution (100,000 IU 4-6 times a day), or miconazole gel; 4 times a day can be administered.

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