

SJOGREN'S SYNDROME-A REVIEW

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Abstract: *Sjogren's syndrome (SS) is a slowly progressive chronic autoimmune disease characterized by chronic inflammation of the exocrine glands. Xerostomia, Keratoconjunctivitis sicca and the B-lymphocytes hyperactivity are the characteristic features of the syndrome. Sjogren's syndrome (SS) also called as "Mikulicz disease" and "Sicca syndrome". Lacrimal and salivary glands are most affected, which leading to mouth dryness and eye dryness. Sjogren syndrome can exist by itself known as primary Sjogren syndrome or associated with another disorders such as systemic sclerosis, rheumatoid arthritis, primary biliary cirrhosis or Hashimoto thyroiditis (associated secondary Sjogren syndrome).*

Keywords: *Xerophthalmia, Sicca syndrome, Autoimmune disorder, Dry mouth.*

1. INTRODUCTION

Sjogren's syndrome was earlier pronounced as 'Shurgren', named after Henrik Sjogren a Swedish ophthalmologist who was first described it in 1933[1]. Sjögren's syndrome is an autoimmune disease that is, a disease in which the immune system acts against body's own cells. In SS, the immune system which targets the moisture-producing glands and causes dryness in the mouth and eyes. Other parts of the body can also be affected which results a wide range of possible symptoms. This syndrome can also affect other glands such as those in stomach, pancreas, and in the intestines and can cause dryness in the places which needs moisture, such as the nose, throat, airways, and skin. Sjögren's syndrome also known as

rheumatic disease. A rheumatic disease which causes inflammation in the joints, muscles, skin, or other body tissue. Sjogren's is also considered as a connective tissue disorder. Connective tissue is the framework of the body that supports organs and tissues (joints, muscles, and skin).

PREVALENCE

Sjogren's syndrome is estimated to affect general population is about 1-3% .[2]The primary SS(pSS) is a disease with a Prevalence which is not exceeding 0.6% of the general population (6/1000).[3]In epidemiologic study, the calculated prevalence of the SS in 705 randomly selected women age ranges from 52-72 years were 2.7%.[4] SS, although a common disorder in Western countries with an estimated prevalence was 3 in 100 .1 in 1000, people has been rarely reported from India.[5] This report shows the rarity of this disease in our geographic region.

ETIOLOGY AND PATHOGENESIS

Eventhough various development and progress in the field of research has been made to unveil the difference in the mechanistic processes underlying the development of SS, the initial triggering events of the SS have yet to be unearthed. Central to pathophysiology of SS is chronic perpetual stimulation of autoimmune system. Both the B cells and T cells are implicated in the pathogenesis of SS, even though the mechanism of underlying humoral and cellular abnormalities are not yet to known.[6,7]It is probably the result of an environmental stimulus which promotes autoimmune reaction in genetically susceptible persons. Infectious such assialotropic viruses which postulates to trigger the syndrome; however, associations with most of the potential viral candidates, which includes the cytomegalovirus and Epstein-Barr virus, they are weak.[8] The putative role of different viruses in the SS can be viewed in the light that salivary glands are a site of latent viral infections.[9] A genetic predisposition to SS has suggested that because of multiple reports of two or more members of the same family they can develop the syndrome. Affected individuals of the different ethnic origins which carries the different human leucocyte antigen susceptibilities.[4] Reduced level of plasma up to 40 - 50% of the dehydroepiandrosterone sulfate, the precursor of the sex steroid hormone which is produced in the adrenal cortex, which has been identified in the SS-affected individuals, comparing to age and the sex matched controls.[11]

CLINICAL FEATURES

GLANDULAR MANIFESTATIONS

XEROSTOMIA

The dry mouth otherwise known as xerostomia which often manifest as the 'cream cracker' sign. It leads to inability to swallow which tend to cause dry dental caries it is the common feature that may prompt a referral from the dentist. About half of the patients complain of therecurrent parotid gland swelling, particularly relatively young patients in whom the inflammatory phase predominates.[12]In an advanced disease, oral mucosa appears to be dry and glazed and tends to form the fine wrinkles. Extreme dryness of the mouth which can causes the tongue to stick on the palate, which may leads to a "clicking" quality in the speech of the patients with SS. In general, the surface of the tongue becomes red and lobulated, with the partial or complete depapillation of the tongue.[13]

OCULAR MANIFESTATIONS

Dry eyes also known as xerophthalmia. Lacrimal gland involvement which leads to diminished tear production and causes destruction of both corneal and the bulbar conjunctival epithelium

and a constellation of the clinical findings termed keratoconjunctivitis sicca (KCS).[14]Symptoms of dry eyes can be include sensations of itching, grittiness, or soreness, even though the eyes' appearance is normal. Ocular complaints which includes photosensitivity, erythema, eye fatigue, decreased visual acuity, a discharge in the eyes, and sensation of a film across the visual field.[13]In more severe form of disease, functional disability with the visual impairment occurs. Complications of KCS includes corneal ulcerations that can leads to perforations and iridocyclitis.[15]

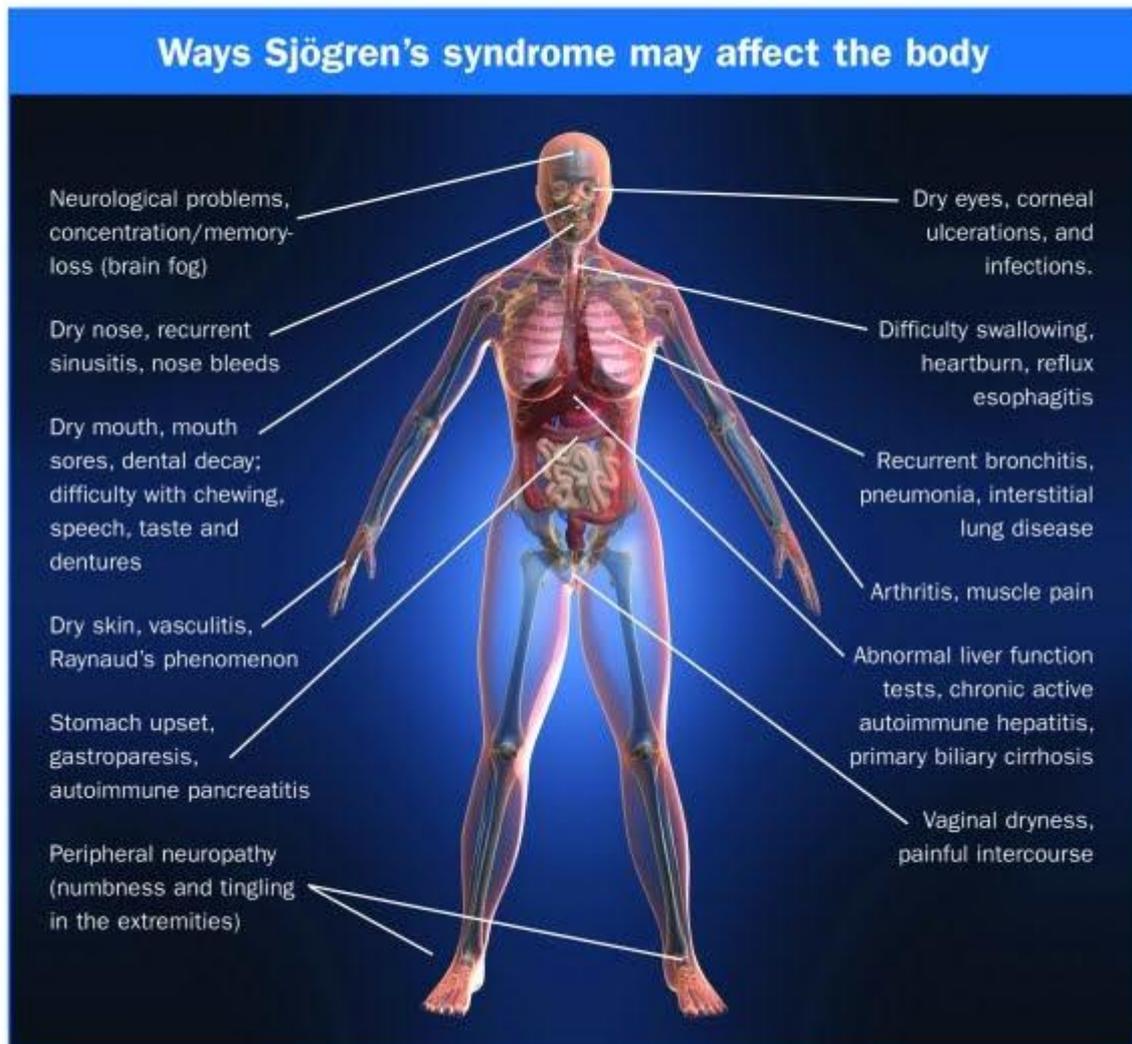
EXTRA GLANDULAR MANIFESTATIONS

In Sjogren's syndrome approximately 50% of the patients having the systemic manifestations which can includes the general constitutional symptoms such as fatigue and low-grade fever, as well as specific organ involvement.Extraglandular manifestations which can be divided into two major groups.The Peri-epithelial organ involvement which may leads to arthritis, interstitial nephritis, liver involvement, and the obstructive bronchiolitis which is the result of the lymphocytic infiltration of affected organs. These features appears early in the disease and usually has a benign course. In contrast, extra-epithelial manifestations such as palpable purpura, glomerulonephritis, and the peripheral neuropathy which is caused by the means of immune complex deposition of the disease and they are secondary to the ongoing B cell hyper-reactivity. These features are usually observed later in the disease and are associated with the increased morbidity and risk for the development of lymphoma.[16]

CLINICAL SYMPTOMS AND SIGNS OF EXTRA GLANDULAR MANIFESTATIONS OF SS

CLINICAL SYMPTOMS AND SIGNS	%
▪ Gastrointestinal symptoms (reflux, dyspepsia, diarrhea, Constipation)	54
▪ Arthralgia or nonerosive arthritis characterized by tenderness, swelling or effusion of peripheral joints	37-75
▪ Autoimmune thyroiditis	15-33
▪ Pulmonary disease (chronic cough, recurrent bronchitis with chronic diffuse interstitial infiltrates on radiography, abnormal spirometry, pulmonary alveolitis or fibrosis on computed tomography)	29
▪ Raynaud's phenomenon	16-28
▪ Cutaneous vasculitis	12
▪ Peripheral neuropathy	7
▪ Lymphadenopathy (enlarged lymph nodes in cervical axillary, or inguinal region)	7
▪ Renal involvement (proteinuria, renal tubular acidosis, interstitial nephritis, glomerulonephritis, abnormal	6

al urinalysis)	
▪ Fever not associated with infectious process	6



DIAGNOSIS

The diagnostic process is not straightforward as many of the symptoms which are subjective and vague and can be dismissed initially as other conditions or effect of medications.[28] Although minor salivary gland biopsy has traditionally considered “the gold standard” for the diagnosis of SS, newer criteria have emerged to assist the identification of the disease. Early recognition of the SS can prevent the complications such as the dental caries, corneal ulceration, chronic oral infection, and sialadenitis, and it also allows for the clinical surveillance to the development of serious extraglandular systemic manifestations.[13]

The revised diagnostic criteria established in 2002 by the American-European Consensus [3]

American-European Consensus Classification Criteria for Sjögren's Syndrome	
I. Ocular Symptoms [at least one]	<ul style="list-style-type: none"> • Symptoms of dry eyes for at least 3 months • A foreign body sensation in the eyes • Use of artificial tears 3 or more times per day
II. Oral Symptoms [at least one]	<ul style="list-style-type: none"> • Symptoms of dry mouth for at least 3 months • Recurrent or persistently swollen salivary glands • Need for liquids to swallow dry foods
III. Ocular Signs [at least one]	<ul style="list-style-type: none"> • Abnormal Schirmer's test • Positive vital dye staining of the eye surface
IV. Histopathology [at least one]	<ul style="list-style-type: none"> • Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥ 1 per 4 mm²)
V. Oral Signs [at least one]	<ul style="list-style-type: none"> • Unstimulated whole salivary flow • Abnormal parotid sialography • Abnormal salivary scintigraphy
VI. Autoantibodies	<ul style="list-style-type: none"> • Anti-SSA (Ro) or Anti-SSB (La), or both

ORAL DIAGNOSTIC TEST

Sialometry

Patients present with clinically overt SS have been reduces the flow rate which measures the submandibular/sublingual flow rates may contribute to an early diagnosis of SS. In contrast, parotid flow rates which are decreased in the SS and Non-SS sicca patients.[17] The Test should be therefore standardized; unstimulated whole saliva collection test is performed for 15 min, and the test was considered positive when <1.5 ml whole saliva were collected.[3]

Sialography

The sialography which is typically shows sialectasias in contrast to fine arborization seen in the normal parotid ductules. Diagnosis is generally based on the classification given in [18]

Sialographic staging

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 (cavitory) refers to contrast media collection ≥ 2 mm in diameter

Stage 4 (destructive) refers to the complete destruction of the gland parenchyma

Scintigraphy

In the scintigraphic test, ^{99m}Tc-pertechnate is given intravenously, and in SS patients the typical finding is decreased uptake in response to the stimulation of parotid and in the submandibular salivary glands. This test is an sensitive and valid method to measures abnormalities in the salivary gland function by the hands of skilled personal.[19]

Sialochemistry

SS is a mixture of the increased inflammatory proteins and the decreased acinar proteins when compared with the healthy controls.[20] Furthermore ionic changes was observed in

theSS affected individuals, they are regarding the levels of chloride, potassium, calcium, sodium and the magnesium.[17]

Magnetic Resonance (MR) and ultrasonography (US)

MR imaging (MRI), MR sialography and the US are noninvasive methodologies that allows the imaging of the salivary glands in their physiological state without the artefacts induced by the intraductal contrast media or by the biopsy procedures. MRI were shown to provide a reliable imaging procedure to evaluate the glandular alterations. It also allows the multiplanar evaluation and processes a high contrast tissue resolution. Characteristically, in SS, MRI reveals an homogeneous internal pattern on both the T1 and T2 sequences, with the multiple hypo- and hyperintense nodules of the different sizes.[21]

Serologic tests

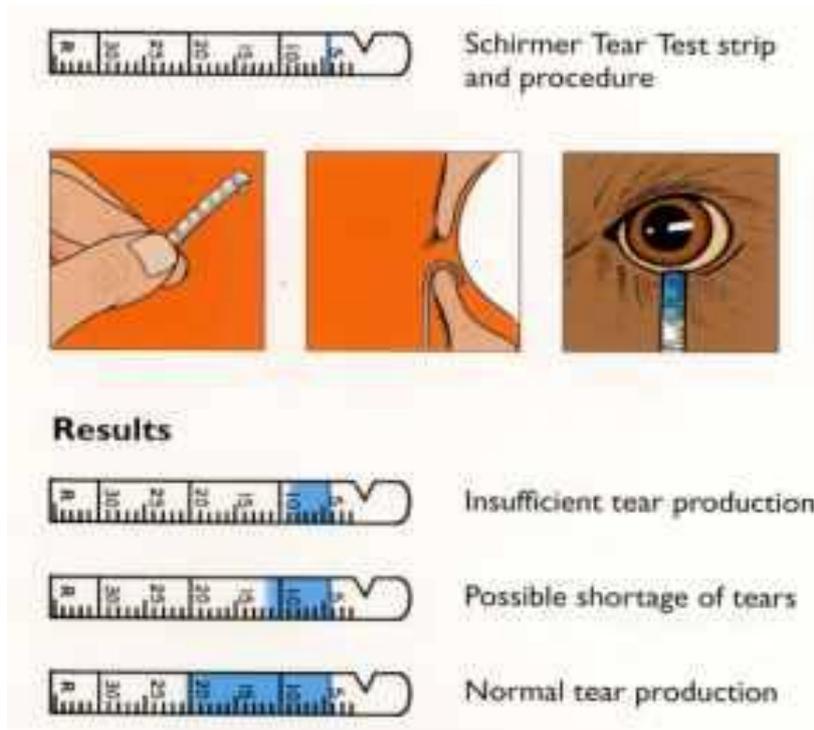
Serology is used to establish the presence of the anti-SS-A/Ro and anti-SS-B/La auto-antibodies, which is based on the enzyme-linked immunosorbent assay. Anti-SS-A/Ro antibodies can be detected in other autoimmune processes such as the rheumatoid arthritis and systemic lupus erythematosus; for this reason, anti-SS-B/La antibodies are considered to be more specific for SS. Anti-SS-A/Ro can also be isolated in 25-65% of cases, and anti-SS-B/La in 13-48%.[22]

Ocular diagnostic tests

1. Schirmer test
2. Rose Bengal Staining
3. Tear break up time (BUT)

1. Schirmer test

The tip of a strip of the filter paper which is 30 mm long is slipped beneath the inferior lid, with the remaining of the paper hanging out. After 5 minutes, length of paper wetted is measured. Wetting of the paper less than 5 mm is the strong indication of diminished tear production.



2. Rose Bengal Staining

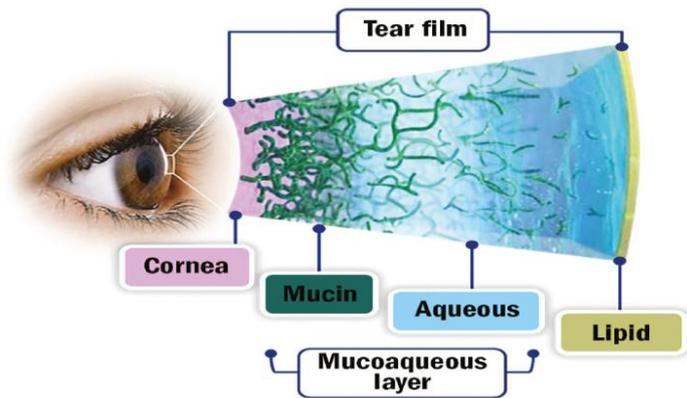
Rose bengal is the aniline compound that stains the devitalized or damaged epithelium of both the cornea and conjunctiva. In Sjogren's syndrome, slitlamp examination after the rose bengal staining shows punctate pattern of filamentary keratitis.



Notice the purple Rose-Bengal staining. The white of the eye normally should not take up any stain. Even though there is no deficiency of tear production, the eye is dry because the tear film is very unstable and breaks easily. There may be increased evaporation of tears as well. The symptoms are of constant eye irritation.

3. Tear Break-up Time:

A drop of fluorescein is instilled into the eye, and the time between the last blink and appearance of dark spot, a nonfluorescent areas in the tear film are measured. An overly rapid break-up of tear film indicates an abnormality of either the mucin or the lipid layer.



HISTOPATHOLOGY

Salivary gland Biopsy is a positive biopsy which is defined as at least one focus of dense, inflammatory infiltrate which contains at least 50 lymphocytes/4 mm². The lip biopsy may be useful in ambiguous cases or when therapy beyond the symptom management is being considered.[23]

Differential Diagnosis

The differential diagnosis of the SS which includes the conditions and medications that can produce KCS, xerostomia, and the parotid gland enlargement [Table 3].[13]

XEROSTOMA

- Amyloidosis
- Diabetes mellitus
- Sarcoidosis
- Viral infections
- Trauma
- Irradiation
- Psychogenic
- Drugs like antihypertensive, parasympatholytic, and psychotherapeutic agents

DRY EYES

- Allergic conjunctivitis
- Blepharitis
- Pemphigoid
- Stevens-Johnson syndrome
- Sarcoidosis
- Toxicity (burns and drugs)

Management

At present, treatment for the SS in most of the patients is essentially symptomatic. The patient should be regularly visit a rheumatologist as well as an ophthalmologist and the dentist in order to prevent and treat the consequences of the mucosal dryness, in addition to extraglandular manifestations and other associated complications of the syndrome [3,24-27]

Management of SS**Topical and systemic management****XEROPHTHALMIA**

- Artificial tears & ointments commercially available preparations of Artificial tears and ocular ointments.
- Hydroxyethyl cellulose(Adsorbotear)
- White petrolatum (Duratears,Lacrilube)
- Polyvinyl alcohol (Hypo Tears ,Liquifilm Forte, Tears plus)
- Polyethylene glycol(AquaSite)
- Hydroxypropyl methylcellulose(Bion Tears, Tears Naturalae)
- Methylcellulose(Murocel)
- Carboxymethylcellulose(Refresh plus)
- Soft contact lenses
‘Puntalocclusion’ by using a variety of ‘plugs’ to occlude the punctal openings at the inner aspects of the eyelids eye for longer time.
- Muscarinic agonists
Pilocarpine(Salagen)-Oral pilocarpine,at a dosage of 5mg twice daily
Cevimeline(Evoxac)-Dosage of 30 mg three times daily
- Anti-inflammatory medications
Steroids
Cyclosporine

XEROSTOMIA

- Maintenance of good oral hygiene
- Use of sugarless sweets and chewing gums to stimulate residual salivary flow
- Artificial salivary products
- Commercially Available preparations of Artificial saliva and oral Lubricants
Salivart
Biotene Mouthwash
Mouthkote
Xero-Lube
Saliment
- Special toothpaste
- Fluoride supplementation
- Eradication of oral candidiasis
- Antimicrobial mouth rinses
- Sugar substitutes-Xylitol
- Pilocarpine-dosage of 5mg four times daily
- Cevimeline at a dosage of 30 mg three times daily
- Natural human interferon alfa-150 IU 3 times daily for 12 weeks
- Nystatin in tablets or solution (100,000 IU 4-6 times a day),or
- Miconazole gel 4 times a day

SYSTEMIC MANAGEMENT

- Corticosteroids (hydroxychloroquine 6-7 mg/kg/day)
- Prednisone (1-2 mg/kg/day)
- Nonsteroidal anti-inflammatory drugs

- Immune regulators
- Immune suppressors reversed for severe cases(azathioprine)

2. CONCLUSION

Sjogren's syndrome is frequently difficult to diagnose because it is often overlaps with the other diseases namely lupus erythematosus, Rheumatoid Arthritis, Scleroderma and Polymyositis. People with SS may be more susceptible to drug allergies and care should be needed to monitor the condition if medication is required. Like all the chronic diseases it is important to have an regular contact with your doctor and eye specialist to monitor your condition. Regular dental checkups are also necessary. Although SS is not life threatening disease careful attention is much needed .

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