Sjögren’s syndrome (SS) is a chronic inflammatory autoimmune disease characterized by mixed cellular infiltration of exocrine glands, notably the lachrymal glands and salivary glands. (autoimmune exocrinopathy). This inflammation causes dryness of the eyes, (xerophthalmia), dryness of mouth (xerostomia) and very frequently dryness of nose, throat and vagina. The combination of dry eyes and dry mouth is often referred to as sicca syndrome. In many cases, these clinical features are associated with other autoimmune diseases. Sjögren’s syndrome is known to be associated with either low or high MALT lymphoma.

**Classification**

Primary Sjögren’s syndrome: comprises the “sicca” syndrome without an associated autoimmune rheumatic disease. Exocrine function seems to be more severely impaired than in the secondary type and primary SS is associated frequently with a variety of extra glandular manifestations.

Secondary Sjögren’s syndrome consists of a sicca complex, which may be relatively mild and associated with one of the autoimmune diseases.

The only conditions where SS may occur are, after radiation therapy to head and neck in Hodgkin’s lymphoma, tuberculosis, sarcoidosis and amyloidosis.

Primary, rarely secondary, Sjögren’s syndrome may be associated with either low or high MALT lymphoma. Monoclonality defines the lymphoid infiltrates specially in parotid gland and stomach where these tumors are prone to occur.

**Prevalence**

In an extensive study done at rheumatic care center at Government General Hospital -Chennai involving 24,500 patients over a period of 20 years 3 cases were found to satisfy criteria for primary Sjögren’s syndrome (0.01%). All the cases were females and mean age was 36.6 years.

In another study 4 from the same center, 9 cases met the criteria for the diagnosis of secondary Sjögren’s syndrome. 8 (2%) out of 400 cases of rheumatoid arthritis and 1 (0.73%) out of 138 cases systemic lupus erythematosus were diagnosed to have secondary SS. None of the patients of progressive systemic sclerosis (98 cases), polymyositis / dermatomyositis, mixed connective tissue disease and polymyositis nodosa had secondary SS. All the patients were females. Average age of onset of SS in rheumatoid arthritis was 38.2 years (range 28 to 59 years) and 23 years in SLE. The mean duration between the onset of RA and development of secondary SS was 5.1 years and for SLE it was 3 years.

### Table 1: Autoimmune diseases that are associated with Sjögren’s syndrome.

<table>
<thead>
<tr>
<th>Chronic active hepatitis</th>
<th>Scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeliae disease</td>
<td>Polymyositis nodosa</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Polymyositis/dermatomyositis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Graves’ disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Graft-versus-host disease</td>
</tr>
</tbody>
</table>

### Table 2: Preliminary criteria for the classification of Sjögren’s syndrome:

1. **Ocular symptoms**
   - A positive response to at least one of the following questions.
     - Have you had daily, persistent, troublesome dry eyes for more than three months?
     - Do you have recurrent sensation of sandy or gravel feeling in the eyes?
     - Do you use tear substitutes more than three times a day?

2. **Oral Symptoms**
   - A positive response to at least one fifth following questions.
     - Have you had daily feeling of drug month for more than three months?
     - Have you had recurrent or persistently swollen salivary glands as an adult?
     - Do you frequently drink liquids to aid in swallowing dry foods?

3. **Ocular signs**
   - Objective evidence of ocular involvement determined on the basis of a positive result on at least one of the following two tests.
     - Schirmer - one test (≤ 5mm in 5 minutes)
     - Rose Bengal score (≥ according to the van Bijsterveld scoring system)

4. **Histopathological findings**
   - Focus score ≥ 1 on minor salivary gland biopsy (focus defined as an agglomeration of at least 50 mononuclear cells; focus score defined as the number of foci/4mm² of glandular tissue).

5. **Salivary gland involvement**
   - Objective evidence of ocular involvement determined on the basis of a positive result on at least one of the following three tests.
     - Salivary scintigraphy
     - Parotid sialography
     - Unstimulated salivary flow (≤ 1.5 ml in 15 minutes)

6. **Autoantibodies**
   - Presence of at least one of the following autoantibodies in the serum.
     - Antibodies to Ro/SS-A or La/SS-B or anti-nuclear antibodies or rheumatoid factor.
   - A patient is considered as having probable SS if three of the six criteria are present and definite SS if four of six are present.

The author has observed one case of primary SS and three cases of secondary SS out of 16,000 patients over 17 years.
Table 3: Clinical features keratoconjunctivitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign body sensation</td>
<td>Dilation of the bulbar conjunctival vessels</td>
</tr>
<tr>
<td>Burning</td>
<td>Mild pericorneal injection</td>
</tr>
<tr>
<td>Tiredness with/without difficulty in opening eyes</td>
<td>Photophobia</td>
</tr>
<tr>
<td>Dry feeling often with inadequate response to physical chemical irritants and emotions</td>
<td>Irregularity of the corneal image</td>
</tr>
<tr>
<td>Redness</td>
<td>Discharge</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Dullness of the conjunctiva and/or cornea</td>
</tr>
<tr>
<td>Itchiness</td>
<td></td>
</tr>
<tr>
<td>Aches</td>
<td></td>
</tr>
<tr>
<td>Soreness</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Inability to tolerate contact lenses</td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES**

Sjögren’s syndrome is associated with a wide variety of clinical features.

Ocular involvement: Patients frequently complain of their eye feeling dry, sore and gritty. They may have difficulty in wearing contact lenses and cutting onions no longer induces tears.

Complications of untreated sicca syndrome results in corneal ulceration, and perforation, leading to uveitis, cataract and glaucoma.

Oral involvement: All patients with Sjögren’s syndrome complain of dryness of mouth, lip cracking, difficulty in mastication, and at times dysphagia. Drying of tongue and absence of salivary pool can cause angular stomatitis, fissuring and ulceration of the tongue, dental caries and candidiasis.

Sialography is a radio-contrast method of assessing anatomical changes in the salivary duct system.

Scintigraphy (isotope scanning) provides a useful functional assessment of the salivary gland for observing the rate, the density of the uptake of 99mTc pertechnate and the time for it to appear in the mouth during a 60-minute period after i.v. injection.

Articular features: 75% of patients with primary Sjögren’s syndrome may complain of arthralgia. Less than 10% have true arthritis.

Dermatological involvement: Annular erythema mainly on the face and trunk, dryness of the skin particularly nasal and vaginal dryness are noted.

Vascular involvement: Raynaud’s phenomenon is present in 35-50% of patients with Sjögren’s syndrome. It is said there are two types of inflammatory vascular diseases in patients with primary Sjögren’s syndrome namely neutrophilic inflammatory vascular disease and mononuclear inflammatory vascular disease. Both types may cause end-organ damage.

Pulmonary involvement: Significant pulmonary involvement is uncommon. Symptoms vary from dry cough to dyspnoea from interstitial lung disease. High resolution CT scan is a useful tool.

Gastro-intestinal involvement: Oesophageal dryness may cause dysphagia. Atrophic gastritis has been recognized as a complicating factor for primary and secondary Sjögren’s syndrome.

Renal involvement: Well-known renal association is renal tubular acidosis. Renal histological examination may demonstrate the infiltration of the tubules and renal parenchyma by lymphocytes and plasma cells.

One study by Alexander et al showed a high proportion (upto 25%) of patients with such serious major central nervous system involvement that they are difficult to distinguish them from patients with multiple sclerosis.

Another study in England and Greece showed that major neurological events in Sjögren’s syndrome are rare.

Endocrine involvement: Hypothyroidism which is clinically apparent is present in 10-15% of patients with Sjögren’s syndrome.

Links to lymphoma: Patients with Sjögren’s syndrome have 44 times increased risk of developing lymphoma as compared to general population.

Most of the lymphomas are low grade B cell lymphomas of the mucosa-associated lymphoid tissue (MALT) type and roost occur within the salivary glands.

The earliest diagnostic feature of this lesion is a proliferation of centrocyte like cells around epithelial islands. These cells meet the criteria for a lymphoid neoplasm since they show light and heavy chain monoclonality, but the monoclonality may antedate the development of lymphoma by many years.

Autoantibodies: Many organ and non-organ specific antibodies may be detected in the patients of both primary and secondary Sjögren’s syndrome.

Both rheumatoid factor and antinuclear antibodies are frequently found in both primary and secondary Sjögren’s syndrome.

The morphological pattern on nuclear immunofluorescence is usually speckled type. Anti-Ro antibodies are associated with early disease onset, recurrent parotid gland enlargement, vasculitis, purpura, hypergammaglobulinaemia, and hypocomplementaemia.

Prognosis: In a study of 112 patients for 10-12 years Kruize et al found that primary Sjögren’s syndrome is characterized by mild and stable course in the majority of cases.

**IMMUNOGENETICS**

Primary Sjögren’s syndrome: An increased association with HLA-Dw3(DR3) and DR52 has been reported.

Patients with antibodies to Ro and La have an increased frequency of HLA DR3.

In contrast a study among secondary Sjögren’s syndrome (most with SLE or RA) only DR 52 was increased.

Aetiopathogenesis: A viral aetiological factor has been considered as playing an important role because the salivary glands are known to be the site of latency for various viruses. The possible mechanisms by which viruses can induce tolerance bypass, include polyclonal activation of B cells, molecular mimicry between viral epitopes and autoantigens, modified self, idiotypic netware perturbation, exposure of so called “hidden antigens” and direct toxic effects of viruses on target cells.

All these mechanisms may be applicable to Sjögren’s syndrome.
Epstein-Barr virus (EBV) and retroviruses have been considered as possible aetiological agents. Endogenous retroviruses can cause interferon-α expression which stimulates epithelial cells to express HLA class II antigens and cytoplasmic La. This, in turn, could induce an immune response resulting in the infiltration of positive CD4 lymphocytes, which can secrete further interferon-α. The view was put forward by Talal that the activator epithelial cells may be the main instigator of autoimmune in Sjögren’s syndrome.

Other aetiological factors
The precise reason why it is principally women who suffer from Sjögren’s syndrome remains unclear. The possible role of abnormalities in apoptosis in patients with Sjögren’s syndrome has been explored in several reports.

Changes in IgA glycosylation are detectable in patients with primary Sjögren’s syndrome has been suggested (Dueymes et al)\(^6\)

**TREATMENT**

The treatment of Sjögren’s syndrome is symptomatic relief of the effects of chronic xerostomia and keratoconjunctivitis. This is achieved by keeping the mucosal surfaces moist. Dry eyes need artificial tears as often as necessary. Hydromellose (Hydroxyethylcellulose) helps to replace aqueous layer.

Acetylcyesteine helps to break down mucus accumulation. Dispersants like dextran, polyethylene glycol spread aqueous layer.

Drugs like anti-hypertensives, diuretics, anti-depressants, decongestants can cause decrease in lachrymation and salivation and should be avoided. Smoking is to be avoided.

Low humidity, air conditioning, dusty, dry and windy atmosphere may exacerbate symptoms.

Regular and proper oral hygiene and frequent dental assessment is required. Topical oral treatment with fluoride may slow down damage to teeth.

Bromhexine (48 mg/day) may help sicca symptoms. Pilocarpine hydrochloride (5 mg three times daily) may also help.

Lubricant jellies are used to treat vaginal dryness.

Dry skin is treated with moisturizing creams.

Parotid gland infection is treated with tetracycline. (500 mg four times a day)

Arthralgia or joint symptoms are treated with non-steroidal anti-inflammatory drugs or simple analgesics.

Hydroxychloroquine (200 mg a day) helps both arthralgia and fatigue of Sjögren’s syndrome. It also reduces hypergammaglobulinaemia, decreases titre of IgG antibodies to La/SS-B, and increases haemoglobin.\(^{20}\)

Corticosteroids (0.5 - 1.0 mg/kg/day) are used in patients with severe extra glandular disease including interstitial pneumonitis, glomerulonephritis, vasculitis, and peripheral neuropathy.

Cyclosporin has been tried with variable results.

Interferon-α increased saliva production in few cases.

High dose intravenous immunoglobulin and plasma exchange have been tried with limited success.

Anti CD4 monoclonal antibodies decrease ocular inflammation in experimental mouse but not salivary gland inflammation.
REFERENCES


