Sjögren's Syndrome

Synonyms: Gougerot's syndrome, sicca complex

Sjögren's syndrome is an autoimmune condition in which there is lymphocytic infiltration of exocrine glands, producing the main symptoms of xerophthalmia (dry eyes), xerostomia (dry mouth) and enlargement of the parotid glands.

The disease is called primary if it develops in isolation and secondary if it occurs with other autoimmune diseases - usually rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or scleroderma. Current thinking has identified a host of factors (eg, immunological, genetic, hormonal and inflammatory) that may be involved in causing the primary syndrome. One theory is that inflammation or dysfunction of the exocrine glands sets up an autoimmune reaction[1].

Epidemiology[2]

Several studies of the epidemiology of Sjögren's syndrome report a prevalence between 0.4 and 0.8%. Prevalence rises with age but age of onset is usually in the 30s or 40s. Rarely, it can occur in childhood. It is up to 20 times more common in women than in men, and men who have the condition tend to be less severely affected by it.

Risk factors

There are as yet no chromosomal regions identified by linkage studies (eg, twin studies) which yield definitive proof of a genetic component but circumstantial evidence is heavily in favour of a genetic aetiology[3]. There is a genetic predisposition for the disease but the HLA association varies among ethnic groups.

Vitamin D deficiency is more common in patients with Sjögren's syndrome[4]. Additionally, complications such as neuropathy and lymphoma may be more likely in patients with vitamin D deficiency[5].

Presentation[6]

History

The most common presenting features are dry eyes and dry mouth. However, these are common complaints and may affect as many as a third of elderly people. Hence, whilst dry eyes and dry mouth are common features of Sjögren's syndrome, most people who present with such symptoms do not have the disease. As well as fibrosis and atrophy of glands predisposing to sicca syndrome in the elderly, they may also be taking drugs with antihistamine or anticholinergic effects. Dry mouth may present with a number of related complaints:

- Difficulty eating dry food, typically cracker biscuits.
- Habit of having a glass of water by the bed at night.
- Altered sense of taste.
- Difficulty with dentures.
- Complaint of the tongue sticking to the roof of the mouth.
- Speaking for long periods of time causes hoarseness.
- Dental and periodontal problems.
- Oral candidiasis and angular cheilitis.

Dry eyes tend to cause a gritty sensation. There is a predisposition to blepharitis and the eyes may be sticky in the morning.
There are a number of other features that can occur with the disease:

- There may be recurrent parotitis, usually bilateral. Glands are usually enlarged but this is not often the presenting feature.
- Dryness of the mucosa of the trachea and bronchi may present as a dry cough. The dryness may predispose to chronic obstructive pulmonary disease, bronchiectasis and interstitial lung disease. Lung involvement occurs in 10-20% of patients [7, 8].
- Dryness of the pharynx and oesophagus may cause difficulty in swallowing; lack of saliva and secretions may predispose to gastro-oesophageal reflux.
- Disease of the pancreas can lead to malabsorption and even acute pancreatitis or chronic pancreatitis but a more likely cause of elevated serum amylase is parotitis.
- Primary biliary cirrhosis and autoimmune hepatitis each occur in around 5% of people with Sjögren's syndrome [9].
- There can be dry skin and vaginal dryness causing dyspareunia.
- Other skin features include purpura and annular erythema. The dry skin is not linked to decreased sebaceous or sweat gland secretion but to a specific alteration of the protective function of the stratum corneum [10, 11].
- Fatigue is a common feature, occurring in 70-80% [12].
- Sleep disturbance occurs in 15%, anxiety in 20% and depression in 40%.
- Chronic pain including myalgia and polyarthralgia occur in 50%.
- About 20% have Raynaud's phenomenon.
- Rare features include polyneuropathy that may be a sensory peripheral neuropathy, cranial neuropathy, usually of the facial or trigeminal nerves, or vasculitis which can produce a mononeuritis multiplex [13].

**Examination**

- Look at the eyes. There may be dilatation of the conjunctival vessels. Look for corneal lesions and gently pull down the lower eyelid to assess the tear pool. There may be blepharitis.
- The mouth may look dry and a wooden tongue depressor may stick to the tongue. There may be evidence of infection including oral candidiasis and dental caries.
- Submandibular glands may be enlarged but more obvious is bilateral enlargement of the parotid glands. A unilateral and hard salivary gland tumour should prompt immediate referral. Other salivary gland disorders may need to be considered.
- There may be features of other autoimmune disorders such as RA, SLE, scleroderma and even primary biliary cirrhosis or chronic hepatitis.

**Associated diseases**

There may be a number of associated autoimmune conditions, such as the variant of scleroderma CREST: calcinosis, Raynaud's phenomenon, oesophageal motility disorder, sclerodactyly and telangiectasia. There may be joint pain, swelling and fatigue or recurrent miscarriage with antiphospholipid syndrome.

**Differential diagnosis**

- Amyloidosis (immunoglobulin-related)
- Bulimia
- Chronic pancreatitis
- Graft-vs-host disease
- Polymyositis
- RA
- Salivary gland tumours
- Sarcoidosis
- Scleroderma
- SLE
- Tuberculosis
- Non-Sjögren's sicca syndrome [14]
Investigations

- FBC is usually normal, although anaemia of chronic disease may be a feature. Abnormal white cell count may suggest a lymphoma. ESR may be raised but is nonspecific.
- Rheumatoid factor is more often positive in Sjögren’s syndrome than it is in rheumatoid disease.
- Antinuclear antibodies are often positive - even without SLE - and there may be positive antiphospholipid antibodies.
- Antibodies against alpha-fodrin and Ro/La autoantigens (antigens related to cell membranes) may be raised in non-Sjögren’s sicca syndrome.
- In the Schirmer test, a bent piece of filter paper is placed into the lower conjunctiva and left there for five minutes. In normal people the paper will be wet to 15 mm or beyond after five minutes, whereas a definitive positive result is less than 5 mm after five minutes. This test can be useful to help exclude or confirm significant dryness of the eyes but it is not specific for the disease.
- Imaging of the salivary glands - one study found that salivary gland ultrasound performed well compared with more invasive diagnostic procedures. For more complex cases, sialography or salivary scintigraphy may assist in diagnosis.
- Scintigraphy may be helpful in identifying non-Sjögren's sicca syndrome. Dynamic magnetic resonance sialography is a new technique which is proving helpful.
- In cases of uncertainty, biopsy of a salivary gland may be required. Usually one of the minor glands from the inner lip is preferred to a parotid. Histology will reveal gland infiltration.
- Creatinine clearance may reduce in up to 50% of patients.
- CT scan should be carried out if it is suspected that lymphoma is developing.
- MRI scan of the salivary glands may help to identify changes associated with chronic sialadenitis.

Diagnostic criteria

The diagnosis of Sjögren's syndrome is based on the Copenhagen criteria and, more recently, American-European consensus criteria. This is a combination of clinical features and investigations. The condition may be suspected when persistent dry mouth or dry eye syndrome develops. Autoimmune screening tests may then reveal a positive rheumatoid factor and/or antinuclear antibodies and the patient is then appropriately referred to a rheumatologist. When presentation is with glandular swelling (commonly parotid glands), referral to a head and neck specialist for consideration of biopsy is appropriate.

Management

Symptomatic treatments such as artificial tears and saliva are well tolerated and help to relieve the most obvious symptoms. Disease-modifying drugs have been used to treat some of the systemic manifestations of the disease but the level of evidence is low and larger-scale trials of the most promising treatments are needed.

Scoring systems are used to evaluate the severity of the condition. There are several scoring systems developed by the European League Against Rheumatism (EULAR) to assess the severity of symptoms and also of systemic involvement. The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) is useful to evaluate the day-to-day effects of symptoms such as xerostomia as well as fatigue and musculoskeletal pain. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) assesses the systemic effects of the disease such as vasculitis and glomerulonephritis. The two facets of Sjögren's syndrome do not always overlap and it is important to establish which aspect of the disease is most concerning.

Anticholinergic drugs should be avoided.

Eyes

Artificial tears should be applied liberally. There are various types and some of the more viscous ones need less frequent application. Patients may try several and see which ones they prefer. If application at intervals of less than four hours is required then preservative-free preparations are preferred to reduce irritation.

Overnight a more viscous preparation such as Lacri-Lube® may be helpful. Oral pilocarpine has been used with some success for ocular as well as oral symptoms. Humidifiers may be helpful.

Severe dryness may require special glasses to improve the humidification of the eyes or temporary or permanent blockage of the puncta (thus preventing tear drainage) by electrocautery or other means.

Mouth

Patients should be encouraged to drink plenty to keep the mouth moist. Artificial saliva is available and pilocarpine tablets are licensed for those who have some residual salivary function. The dose is 5 mg tablets to be taken four times daily, before each meal and at night.
Saliva contains IgA and other anti-infective agents and so attention to dental hygiene is required and periodic use of antiseptic mouthwash may be beneficial. Topical fluoride and avoidance of sugars are recommended.

A possible role for immunosuppressant agents (e.g., cyclophosphamide) in the relief of ocular and oral symptoms has been identified. Trials involving anti-tumour necrosis factor (anti-TNF) alpha inhibitors have been disappointing but those involving the use of B-cell depleting agents (e.g., rituximab) have been more encouraging.[30, 31]

**Other features**

Vaginal lubricants may be required and infections such as vaginal candidiasis are more likely. Dry skin may benefit from emollients. Hydroxychloroquine may be useful in suppressing arthralgia and skin symptoms.

**Complications**

- Associated autoimmune diseases may become manifest and need management.
- Approximately 50% of patients develop disease in sites other than glands. This could be either lymphocytic invasion of the epithelial cells in lung, liver, or kidney, or as skin vasculitis, peripheral neuropathy, glomerulonephritis and low C4 levels - conditions which represent an immune complex-mediated disease.[32]
- Infections of the eyes and mouth are more likely. The parotid gland may be infected with *Staphylococcus* spp., *Streptococcus* spp. or pneumococcus.
- Watch out for parotid tumours in a hard, unilateral gland.
- Some, but not all, studies have found an increase in the risk of developing non-Hodgkin’s lymphoma, usually around seven or eight years after diagnosis.[33]

**Prognosis**[32]

Prognosis is generally good unless the condition is part of an associated disorder. There is, however, considerable morbidity. Patients with a low C4 count have a high risk for development of non-Hodgkin’s lymphoma and have a worse prognosis with higher mortality rates.

**Historical**

Henrik Samuel Conrad Sjögren (1899-1976) was a Swedish ophthalmologist. He graduated in medicine from the Karolinska Institutet in 1922. He married the daughter of a prominent ophthalmologist from Stockholm and became interested in the subject. He described his syndrome in 1933 in his doctoral thesis ‘Zur Kenntnis der Keratoconjunctivitis sicca’ but it was not of a sufficient standard for him to be awarded the title of ‘docent’ and this denied him a career in academic ophthalmology. The paper was translated into English in 1943 and the eponym became part of the English language. In France the term Gougerot’s syndrome was used, as in 1925 he had described Henrik Samuel Conrad Sjögren; whonamedit.com


28. The British Society for Rheumatology guideline for the management of adults with primary Sjogren’s Syndrome; British Society for Rheumatology (2017)


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