Sjögren's syndrome

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Sjögren's syndrome (SS) is an autoimmune rheumatic disorder characterised by chronic lymphocytic infiltration of the secretory glands with reduced gland function, leading to dryness of the mucosal surfaces, in particular the eyes and mouth.[1] This article will focus on key clinical aspects and attempt to provide a simple guide to management.

Classification

Patients with SS are typically subdivided into two groups:

1 Primary SS (PSS) which exists as a disorder in its own right.

2 Secondary SS which usually develops about 10 years after the onset of an associated rheumatic disorder such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, primary biliary cirrhosis etc.

It is rare for patients to develop PSS and then go on to develop classic RA, for example, but when this does happen it can cause some diagnostic uncertainty. Patients with PSS may present with an inflammatory arthritis which can be misdiagnosed as a mild RA. This confusion is not entirely surprising since the frequency of rheumatoid factor positivity is as high in PSS as in RA. This inflammatory arthritis is typically non-erosive and the correct diagnosis is often reached when the patient reports dryness symptoms (eg dry eyes and/or dry mouth) and is found to have positive anti-Ro/La antibodies (previously called anti-SSA and anti-SSB).

The histology of the glands is similar in primary and secondary SS (described in more detail below) with some important serological differences. In particular, anti-Ro and anti-La antibodies are found in about 70% and 30% of patients with PSS, respectively. It is uncommon to find anti-La antibodies alone. There is no association between these antibodies and the secondary SS of RA and scleroderma. SLE is more complex because these antibodies are found in some patients with SLE and there is an association with SS and subacute cutaneous lupus.

These serological differences are rooted in HLA associations. Over 90% of patients with high anti-Ro and anti-La antibody titres will be HLA-DR3 positive. No such HLA association exists in anti-Ro/La negative PSS patients or patients with RA or scleroderma who have secondary SS.

Apart from this HLA association the aetiology of SS is essentially unknown, although speculation has generally focused on viral infections such as Epstein-Barr virus. Hepatitis C can produce an SS like picture.[2] The hepatitis C virus is rare in PSS patients in northern Europe but might lend some support to the idea of an unidentified virus as a cause for PSS.

Other serological features in patients with PSS can include various combinations of hypergammaglobulinaemia, cytopenias, low complement C4 and antinuclear antibody positivity. For example, some patients with classic primary SS who are anti-Ro/La positive and who often have a particularly systemic form of the disorder have low complement C4 levels and positive anti-dsDNA levels and can be difficult to distinguish from mild SLE.

These clinical and serological observations have been formalised by Vitali *et al*[3] into classification criteria for primary and secondary SS (the American-European Consensus Criteria) (Table 1). They comprise questions about three specific ocular and three specific oral symptom questions (Table 2):

- abnormalities of dryness tests
- a labial gland biopsy showing focal periductal infiltration, and/or
- anti-Ro/anti-La antibodies.

To fulfil the criteria for PSS, patients must have a positive biopsy and/or either or both anti-Ro/La antibodies. This is important as it enshrines evidence for an immune-mediated aetiology in the classification criteria.

Key Points

Sjögren's syndrome (SS) is easily missed or misdiagnosed so be alert to the possibility in any middle-aged or older female patient with a positive rheumatoid factor. Schirmer's test and unstimulated salivary flow rate are easy to check in a routine clinic

Anti-Ro and anti-La antibodies should be checked in any patient suspected of having primary SS (PSS) but these are not helpful in patients with secondary SS

Labial gland biopsy may be needed to confirm the diagnosis in PSS patients who do not have anti-Ro or anti-La antibodies. This should be performed by an expert. Chronic sialadenitis is a normal finding and a positive biopsy requires at least one peri-ductal focus of 50 lymphocytes per high powered field

Simple approaches to treatment of dry eyes and dry mouth can be effective with oral gels and pastilles and artificial tears used as often as needed with preservative free preparations if frequent use is required. Pilocarpine is available to stimulate residual gland function

Hydroxychloroquine or low dose prednisolone may be used for systemic features. Peripheral neuropathy is particularly common and motor involvement may require immunosuppressant treatment. There is a 44-fold increased risk of salivary gland lymphoma so chronic smooth enlargement of the salivary glands or lymphadenopathy needs to be investigated further

KEY WORDS: classification, diagnosis, Sjögren's syndrome, therapy

Differential diagnosis and terminology

A number of medications (eg antidepressants, diuretics) can produce a dry mouth. Other exclusions/differential diagnoses include hepatitis C, HIV (which can cause swollen salivary glands due to CD8 cell infiltration), sarcoidosis (granulomatous salivary gland infiltration), graft-versus-host disease, primary lymphomas and salivary gland swelling (resulting from anorexia or diabetic sialosis).

Some patients will have symptoms of dry eyes and dry mouth but without objective findings (symptomatic xerostomia and/or symptomatic dry eyes). The term xerophthalmia is sometimes used for dry eyes, although technically it refers specifically to the eye features of vitamin B deficiency. Others will have symptomatic and objective dry eyes and/or dry mouth but without anti-Ro/La antibodies and negative gland biopsy (sicca syndrome) or, if they have declined a labial gland biopsy, 'sicca syndrome/possible Sjögren's syndrome'.

Moutsopoulos *et al*[4] have also proposed a further subdivision of PSS into:

- *type 1*: patients with a more 'systemic' picture, typically with anti-Ro/La antibodies, palpable purpura and low C4 levels who are most prone to develop cryoglobulinaemia and/or B cell lymphoma.
- *type 2*: patients with a predominantly glandular form of the disease.

Table 1. The American-European classification criteria for Sjögren's syndrome.

1	Ocular symptoms for >3 months: positive response to at least one of the three European ocular screening questions*
2	Oral symptoms for >3 months: positive response to at least one of the three European oral screening questions*
3	Ocular test: positive Schirmer's test (≤5 mm in 5 min), Rose Bengal score or other ocular dry score (eg lissamine green)
4	Oral test: abnormal result for unstimulated whole salivary flow (≤1.5 normal salivary scintigraphy or parotid sialography
5	Histopathology: abnormal labial-gland biopsy (focus score ≥1)
6	Auto-antibodies to Ro (SSA), La (SSB) or both

Primary Sjögren's syndrome:

- in the absence of potentially associated disease, if any four of the six criteria indicates PSS, as long as either the labial-gland biopsy and/or anti-Ro/La antibodies are present
- alternative criteria for PSS are three positive results for four objective assessments (ocular signs, oral signs, labial-gland biopsy and antibodies)

Secondary Sjögren's syndrome:
Patients with other connective tissue disease, such as RA, the presence of at least one symptom (1 or 2) plus two of three objective assessments (3, 4 or 5) (ie excluding antibodies) may be considered as indicative of secondary Sjögren's syndrome

Exclusions:
Current use of anticholinergic drugs, previous head and neck radiation treatment, hepatitis C infection, AIDS, pre-existing lymphoma, sarcoidosis or GvH disease

*see Table 2.
GvH = graft-versus-host disease; PSS = primary Sjögren's syndrome; RA = rheumatoid arthritis.

Table 2. The European classification criteria for ocular and oral symptoms: screening questions.

Ocular symptoms	Have you had daily, persistent dry eyes for >3 months? Do you suffer from a recurrent feeling of sand or gravel in the eyes? Do you use artificial tears >3 times a day?
Oral symptoms	Have you felt dryness in your mouth daily for >3 months? Have you had persistent or recurrent episodes of swollen salivary glands as an adult? Do you need to drink liquids frequently when swallowing dry food?

A positive response to one of the three questions should be present for a positive response with each symptom.

Clinical assessment

The more sophisticated tests for ocular dryness such as the Rose Bengal/lissamine green dye test require a slit-lamp and an experienced operator (usually an ophthalmologist), while the more specialist oral tests require a radiologist or access to nuclear medicine. It is possible to do simple but useful tests in the routine clinic. Many outpatient facilities will have Schirmer (blotting paper) test strips, commercially produced standardised strips that can be placed on the conjunctival mucosa of the lower eyelids for five minutes. Wetting of 5 mm or less indicates significant eye dryness. Similarly, an unstimulated salivary flow rate can be measured over 15 min by asking the patient to 'drool' into a plastic pot: 1.5 ml or less collected is typical of SS. In practice, what often happens in the routine setting is measuring for 5 min and multiplying by three.

Some patients with severe SS will not be able to produce tears or saliva in any circumstances, but others can still cry despite having very dry eyes. This is because the mechanisms differ for continuous basal secretion and for acute stimulated secretion of tears and saliva. The ability to cry suggests that not all patients with SS have glandular destruction as the reason for their dryness. A better understanding of this functional rather than structural problem may lead to new therapies. Antimuscarinic receptor antibodies are currently a proposed explanation for this functional impairment.[5]

Histopathology

Historically, labial gland biopsy from inside the lower lip has been used for

diagnostic purposes. This area is easy to access and a superficial incision gives access to large numbers of glands that can be removed without functional impairment. It should be performed by an experienced individual, both to ensure an adequate sample and to avoid damage to the mental nerve (which can give rise to permanent pain/numbness in the affected area). A wedge biopsy is more likely to damage the nerve than a fine dissection.

The gland structure is often described as being like a bunch of grapes, with the acini (the clusters of cells producing the basic saliva) clustered around tubular ducts into which the saliva is secreted, the ducts coming together into larger structures before connecting with the oral cavity. The hallmark of SS is the formation of foci of 50 or more lymphocytes clustered around the ducts. For a 'positive' biopsy, at least one such focus must be seen in a 4 mm^2 section of a high-powered field. False negatives can occur due to sample variation or an inadequate sample or number of cuts through the biopsy. Scattered lymphocytes and plasma cells are seen in a normal gland, often described as 'chronic sialadenitis'. This should not be reported as 'compatible with SS'.

Treatment

Simple approaches such as oral hygiene and regular dental checks are important. Decreased saliva production results in dental caries and more frequent infections in the mouth including candidiasis. Standard strength antiseptic mouthwashes will sting with a dry mouth but milder ones or diluting standard ones can be used. Patients often carry a bottle of water around with them.

Exocrinopathy/sicca manifestation

Some patients find sprays helpful but in most cases the effects last only a few minutes. 'Saliva replacement' gels such as Biotene or Bioextra seem more useful. A much wider selection of topical gels can be found on the internet, particularly in North America. If residual gland function is present, a stimulant such as a citrus or fruit flavoured pastille can help (eg salivix/saliveze pastilles).

Pilocarpine, a muscarinic agonist is licensed for treating SS. The effective dose in clinical trials was 5 mg qds. It has potential side effects such as flushing and urinary symptoms which may limit its use. These symptoms often resolve, however, with continuous use. One suggestion is to start at a very low dose, for example 2.5 mg bd (half a tablet twice daily), increasing by small increments at intervals of 4–8 weeks, waiting for any side effects to wear off before increasing to the next dose. Cevimeline is an alternative but it is not licensed in Europe.

Artificial tears can be used as often as needed, but if required more than 4–6 times a day preservative-free preparations are recommended as the preservative itself can be irritating if used too often. If hypromellose is inadequate, a thicker carbomer can be substituted. Topical steroids are not advised because of the risk of infection. Paraffin based ointments can be used at bedtime. Ciclosporin drops are licensed for use in the USA but not in Europe. In advanced cases of dry eyes, punctal occlusion with a variety of plugs has been used.

Some interest has been shown in autologous transfer of salivary glands to the conjunctiva.[6] Electrical stimulation of saliva production by intra-oral devices is another area under investigation.

Systemic manifestations

Fatigue is commonly experienced by patients with PSS[7] often coupled with myalgia and arthralgia, with fibromyalgia in about 5% of patients. It is important to note that fatigue may be a result of interrupted sleep as the patient may have to void several times at night because of the excess intake of fluids to avoid dry mouth. Medications such as amitriptyline can worsen the sicca symptoms. Arthritis is usually mild, nonerosive and non-deforming. Raynaud's phenomenon is also common.

Leukocytoclastic vasculitis (typically presenting as an intermittent purpuric rash on the lower legs) is sometimes associated with cryoglobulins; patients may have low complement C4 levels. Hydroxychloroquine is often used as a first-line treatment for fatigue, joint pains and purpura. If this is insufficient, some patients will benefit from low-dose oral prednisolone.

Functional involvement of the gastrointestinal system is common, with irritable bowel syndrome, dysphagia and dyspeptic symptoms treated symptomatically.

Renal involvement is uncommon other than subclinical distal tubular acidosis.

The nervous system is commonly involved. About 20% of patients may develop a sensory polyneuropathy.[8,9] Analgesia and hydroxychloroquine may be sufficient. In more severe forms with a progressive sensory/sensorimotor polyneuropathy or if the central nervous system is affected, treatment with cyclophosphamide[10] or mycophenolate has been used. Antitumour necrosis factor α is not effective[11,12] but new biologics such as rituximab[13] and B-lymphocyte-(BlyS)-modulating agents may prove more useful.

B-cell lymphoma (usually the mucosa-associated lymphoid tissue (MALT)) is increasingly reported in PSS and it is thought there is around a 44-fold increased risk. These patients may have a low-grade fever, anaemia, lymphopenia and hypocomplementaemia. Lymphadenopathy, parotid swelling, peripheral neuropathy and cutaneous vasculitis are more frequent than in the general PSS population.

Conclusions

SS is characterised by sicca symptoms, most typically dry eyes and mouth, and diagnosed using the American-European Consensus Criteria. Histologically, the hallmark of SS is focal lymphocytic infiltration around the salivary ducts. Primary SS is associated in 70% of cases with anti-Ro/La antibodies. Differentiation of primary from secondary SS is made on the presence or absence of other associated connective tissue disorders. Treatment is largely symptomatic, but awareness of the available treatments for sicca symptoms, aggressive treatment of neurological involvement and awareness of the increased risk of B cell lymphoma

can make a significant difference to patient care.

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