Sjögren's syndrome

ABSTRACT

This review discusses important aspects of the diagnosis and management of Sjögren's syndrome, covering clinical features, diagnosis and management, and summarizes recent developments in diagnosis, prognostication and treatment.

Sjögren's syndrome is the second most common autoimmune rheumatic condition. It is characterized by lymphocytic infiltrate of the exocrine glands, resulting in dysfunction and destruction. The salivary and lacrimal glands are predominantly affected, giving rise to dry eyes and dry mouth. It is a heterogenous condition and systemic involvement can occur. Sjögren's syndrome is associated with an increased risk of lymphoid malignancy. It is under-recognized, and symptoms can be debilitating to patients.

Sjögren's syndrome is either classified as primary Sjögren's syndrome (occurring alone) or secondary Sjögren's syndrome, which occurs alongside another systemic autoimmune disease, commonly rheumatoid arthritis, systemic lupus erythematosus or scleroderma.

Clinical features

A typical patient with Sjögren's syndrome presents with dry eyes, mouth, tiredness and joint pains. Blood tests classically show mild anaemia, high erythrocyte sedimentation rate, high IgG levels with positive antinuclear antibody (ANA), Ro and/or La autoantibodies. Complement studies reveal low C4 levels.

Sicca symptoms

Sjögren's syndrome is nine times more common in women than men, and usually presents around or after the menopause, although it can develop at any age. Although many doctors discuss 'dry eyes' as a symptom, patients more commonly report grittiness, ocular discomfort, photosensitivity and contact lens intolerance. The eyes may be reddened and shallow erosions of the conjunctiva can occur. The Schirmer's test (*Figure 1*) confirms reduced lacrimal exocrine function and keratoconjunctivitis sicca.

Oral dryness results in difficulty swallowing dry food without a drink, and waking at night for sips of water. Dysphagia can result from xerostomia. A diminished sublingual salivary pool is seen on oral examination. Dry fissured or red atrophic tongue, angular stomatitis, oral candida and dental caries can also be seen. Parotid and submandibular gland swelling are not uncommon (Napeñas and Rouleau, 2014).

Dry nose, dry cough and dry skin are also seen. Vaginal dryness causes dyspareunia.

Systemic manifestations

Sjögren's syndrome is a systemic disease, and fatigue is the most prominent and disabling symptom. Fibromyalgia is also very common. Systemic manifestations can mimic occult malignancy with symptoms including weight loss, anaemia and fever. Arthralgia is common. Arthritis is usually non-erosive and not deforming. Myopathy may also occur. Raynaud's phenomenon, purpura and vasculitic rashes are also seen.

Peripheral nervous system involvement is among the most common extraglandular manifestations, particularly sensory neuropathies. Mononeuritis multiplex, cranial and autonomic neuropathies occur less commonly (Birnbaum, 2010). CNS involvement is much less frequently seen and can mimic multiple sclerosis. Cognitive dysfunction is common. Depression also occurs.

Respiratory involvement includes upper respiratory tract and large and small airways disease. Interstitial lung disease also occurs – lymphocytic interstitial pneumonitis is strongly associated with Sjögren's syndrome (Lynch, 2009).

Interstitial nephritis can cause renal tubular acidosis, nephrogenic diabetes insipidus and symptomatic hypokalaemia. It may also cause interstitial cystitis with symptoms of urinary tract infection and negative urine cultures.

Pericarditis and myocardial disease may occur. Dysphagia, nausea, epigastric pain and dyspepsia are common. Chronic atrophic gastritis also occurs, associated with primary biliary cholangitis and autoimmune hepatitis.

Women with anti-Ro antibodies are at risk of having babies with neonatal lupus, which can cause a congenital heart block.

There is an association with autoimmune thyroid disease and coeliac disease as well.

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Table 1. Risk factors associated with the development of lymphoma

Palpable purpura
Lymphopenia
Low C4
Cryoglobulins
Lymphadenopathy
Persistent salivary gland enlargement
Cutaneous vasculitis

The risk of lymphoma is markedly increased in patients with Sjögren's syndrome, with 5–10% lifetime risk, usually in those with significant immune dysregulation. Lymphadenopathy in the neck or salivary gland swelling could indicate this. *Table 1* shows the risk factors associated with the development of lymphoma.

Mortality is mainly related to systemic involvement and haematological cancer.

Sjögren's syndrome can occur as an overlap autoimmune condition alongside other forms of connective tissue disease, including myositis, systemic lupus erythematosus or scleroderma. Primary Sjögren's syndrome can also present with non-sicca (systemic) manifestations.

Diagnosis

There is often a considerable delay between symptom onset and diagnosis, which may in part be a result of the variability of presentation. The most widely accepted current classification criteria for Primary Sjögren's Syndrome are the American-European Consensus Group criteria (Vitali et al, 2002) (*Table 2*). The 2016 American College of Rheumatology - European League Against Rheumatism criteria have also been published (Shiboski et al, 2017). The population described by both criteria is very similar.

The American-European Consensus Group criteria give three useful questions for evaluating the severity of both oral and ocular symptoms. Patients need to answer one of each set of questions positively to fulfil that criterion.

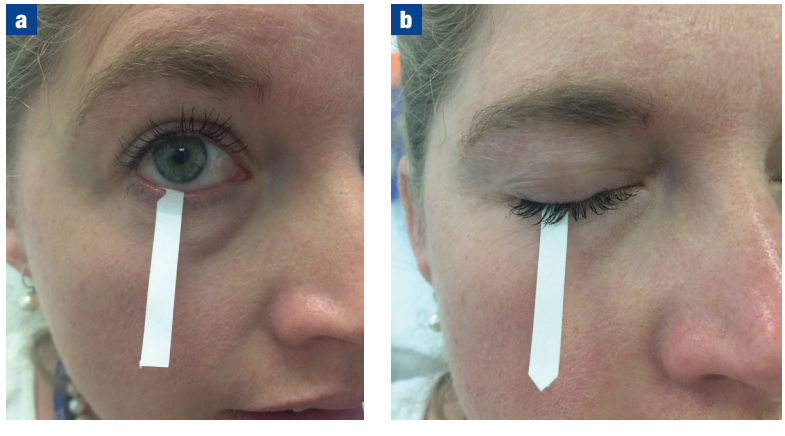
Assessment of ocular signs can be performed in an outpatient clinic. Keratoconjunctivitis sicca is confirmed using the Schirmer's test (*Figure 1*). A positive test is ≤5 mm of wetting, when a standard strip of filter paper is located at the junction of the middle and lateral thirds of the inferior conjunctival sac over 5 minutes.

Conjunctival epithelial damage can be assessed with ocular dye tests. Rose Bengal scoring evaluates the intensity of staining in the conjunctiva and cornea. Fluorescein and lissamine green staining are also used. Fluorescein is used to assess tear break up time in the assessment of ocular involvement.

Table 2. Revised international classification criteria for Sjögren's syndrome

For a definite diagnosis the criteria require four out of six of the following (or three out of the four objective domains*) including at least one of items IV or VI of:
I – Ocular symptoms – at least one of the following symptoms: ■ Have you had daily, persistent troublesome dry eyes for more than 3 months? ■ Do you have a recurrent sensation of sand or gravel in the eyes? ■ Do you use tear substitutes more than three times per day?
II – Oral symptoms – at least one of the following symptoms: ■ Have you had daily feeling of dry mouth for more than 3 months? ■ Have you had recurrent or persistent swollen salivary glands as an adult? ■ Do you frequently need to drink liquids to aid in swallowing dry food?
III – Ocular signs* – positive result from at least one of the following tests: ■ Schrimer's test, performed without anaesthesia (≤5 mm in 5 minutes) ■ Rose Bengal score or other ocular dye score (≥4, according to van Bijstervald's scoring system)
IV – Histopathology* – in minor salivary glands (biopsied from normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1 (defined as the number of lymphocytic foci containing more than 50 lymphocytes, adjacent to normal-appearing mucous acini, per 4 mm^2 of glandular tissue)
V – Salivary gland involvement* – positive result from at least one of the following tests: ■ Unstimulated whole salivary flow (≤1.5 ml in 15 minutes) ■ Parotid sialography showing the presence of diffuse sialectasis ■ Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
VI – Autoantibodies* – serum presence of the antibodies to Ro (SSA) or La (SSB), or both, in the serum
Exclusion criteria: past head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency syndrome, pre-existing lymphoma or sarcoidosis, graft *vs* host disease, use of anticholinergic drugs
From the American-European Consensus Group Criteria (Vitali et al, 2002)

Figure 1. Schirmer's test technique. a. Fold the sterile Schirmer's test paper at the mark (notched). Gently pull down the lower lid with the patient looking up. b. Hang the folded portion of the test strip from the lateral third of the lower lid margin, and leave in situ with the patient's eyes shut. After 5 minutes, remove the strip, and measure the length of the moistened area from the notch.



> Parotid sialography is a contrast media X-ray study of the salivary glands and ducts and has a high diagnostic accuracy in Sjögren's syndrome when diffuse sialectasis is demonstrated.

Minor salivary gland biopsy remains an important diagnostic procedure for Sjögren's syndrome. This procedure is usually done by an oral physician or an oral surgeon under local anaesthetic. A small incision is made in the internal aspect of the lower lip to remove around five minor salivary glands from normal-appearing mucosa. The incision is closed with absorbable sutures. It is a minor day case procedure, which is generally well tolerated with a low rate of complications.

The key histopathological finding is a periductal lymphocytic infiltration. The inflammatory infiltrate is quantified and a cluster of over 50 lymphocytes per 4 mm^2 is termed a focus. It is also useful in excluding other causes of oral dryness (*Table 3*).

Assessment of salivary gland involvement can also be performed in an outpatient clinic. For assessment of unstimulated whole salivary flow, the patient drools passively into a collection receptacle to quantify the volume of saliva produced.

Parotid sialography is a contrast media X-ray study of the salivary glands and ducts and has a high diagnostic accuracy in Sjögren's syndrome when diffuse sialectasis is demonstrated. However, it can be technically challenging, time-consuming and uncomfortable with risk of structural damage or infection. Scintigraphy is a non-invasive method of evaluating the function of the salivary glands using radiolabelled tracer material, but it is usually only available in specialist centres and is relatively insensitive.

Changes in the major salivary glands can be seen on both magnetic resonance imaging and ultrasound, and have specific radiological features which can aid diagnosis.

Serological and laboratory abnormalities are common in patients with Sjögren's syndrome, and include high erythrocyte sedimentation rate, cytopenias (anaemia, leucopenia and thrombocytopenia), hypergammaglobulinaemia, low C4 levels and positive autoantibodies. Monoclonal gammopathy and cryoglobulins are less commonly seen. Antibodies to Ro (SS-A) and La (SS-B) are required for the classification criteria. These are part of the ENA panel done when an ANA is positive although some patients may have anti-Ro and La antibodies despite a negative ANA screening. Rheumatoid factor is often also positive.

The American-European Consensus Group Criteria also included exclusion criteria, as several other common conditions and treatments can mimic Sjögren's syndrome. *Table 3* shows differential diagnoses to consider – several of these conditions need to be excluded before classification with the American-European Consensus Group criteria. *Table 4* shows medications which are associated with sicca symptoms.

Disease monitoring

Patients are generally followed up by a rheumatologist, with clinical assessment for overlap autoimmune disease and manifestations of severe and systemic disease.

Patients with stable disease limited to sicca symptoms may require only annual evaluation by a GP or rheumatologist,

Table 3. Differential diagnoses to consider

Age-related sicca
Drugs (*Table 4*)
Bulimia nervosa
Diabetes mellitus, diabetes insipidus
Chronic viral infection (hepatitis C, HIV and HTLV-1)
Sarcoidosis
Amyloidosis
Head and neck radiation
Lymphoma
Graft *vs* host disease
IgG4-related disease
Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)

Table 4. Medications causing sicca symptoms

Anticholinergic drugs (atropine, scopolamine)
Selective serotonin-reuptake inhibitors
Tricyclic antidepressants
Sympathomimetic drugs (ephedrine)
Benzodiazepines
Phenothiazines
Antihistamines
Nicotine
Opioids
α-1 antagonists (terazosin and prazosin)
α-2 agonists (clonidine)
β blockers (atenolol, propranolol)
Diuretics
Retinoids

while those with extra-glandular manifestations should be evaluated more frequently by a rheumatologist.

Blood tests can be used to monitor for cytopenias, renal, liver and thyroid function, and bone profile. Urine pH and dipstick analysis, serum pH and bicarbonate are used to monitor for renal tubular acidosis.

Assessment of lymphoma risk incorporates risk factors (*Table 1*), assessment of symptoms (including weight loss and fevers) and examination for lymphadenopathy and salivary gland swelling. Autoantibodies, cryoglobulins and lactate dehydrogenase are useful for assessing lymphoma risk. Imaging and biopsy of suspicious lesions should be performed.

Regular ocular assessment by an ophthalmologist and oral hygiene monitoring by a dentist is generally also recommended.

Chronic inflammatory disease is associated with an increased risk of cardiovascular disease (although this has not been confirmed with Sjögren's syndrome) and modifiable cardiovascular disease risk factors may also be addressed.

Treatment

No treatment has been shown to modify the progression of Sjögren's syndrome, so treatment is generally symptomatic.

Oral symptoms

It is essential to maintain good oral hygiene because of the accelerated formation of dental caries. Sugar-free sweets and chewing gums can be used to stimulate residual salivary flow. Artificial salivary products are also available as sprays and gels. Muscarinic agents such as pilocarpine and cevimeline (the latter not available in the UK) can help oral and ocular dryness.

Ocular symptoms

Artificial teardrops and ointments can provide symptomatic relief. Preservative-free preparations are often needed. Blepharitis may complicate Sjögren's syndrome and is treated with lid hygiene. Punctal occlusion is a mechanical treatment to block the tear drainage. Topical corticosteroids or ciclosporin are also used for ocular inflammation. Topical autologous serum may improve objective and subjective measures of dryness, but is only available at specialist centres. Consensus guidelines have been published in the USA for management of dry eye associated with Sjögren's syndrome (Foulks et al, 2015).

Vaginal symptoms

These can be managed with non-hormonal moisturisers. Local hormone replacement therapy is helpful in post-menopausal women.

Psychological symptoms

Psychological symptoms are most effectively managed with self-care measures and exercise (Vivino et al, 2016).

“Regular ocular assessment by an ophthalmologist and oral hygiene monitoring by a dentist is generally also recommended.”

Goal setting and physiotherapy may be useful for fatigue. Exercise has been shown to reduce fatigue and depression.

Systemic treatments

- Hydroxychloroquine is the first-line treatment for musculoskeletal pain and mild inflammatory arthritis associated with Sjögren's syndrome (Gottenberg et al, 2014). There is some weak evidence that it reduces fatigue (Brito-Zerón et al, 2013).
- Steroids, either intermittent short courses of oral or intramuscular for systemic flares and significant organ manifestations with or without additional immunosuppressive treatment, are used. Low dose oral prednisolone is also used for persistent constitutional symptoms in patients with inadequate response to other immunosuppressants.
- Methotrexate is used for inflammatory arthritis.
- Azathioprine, mycophenolate and cyclophosphamide have been used for systemic complications such as lung disease, cytopenias, vasculitis, myelopathy and neuropathy.
- Pilot studies involving anti-tumour necrosis factor-α were promising but have since failed to show improvement of subjective measures.
- Rituximab may be considered for severe systemic disease. Clinical trials did not confirm its efficacy for dryness or tiredness (Devauchelle-Pensec et al, 2014).

Recent developments

The British Society of Rheumatology and British Health Professionals in Rheumatology guidelines group for Sjögren's syndrome has recently developed the UK guidelines for the management of Sjögren's syndrome which have just been published (Price et al, 2017).

The UK Primary Sjögren's Syndrome Registry is a national research biobank of people with primary Sjögren's syndrome. It facilitates clinical trials and academic research studies. It is an initiative of the UK Sjögren's Interest Group and funded by the Medical Research Council (Ng et al, 2011).

The Big Data Sjögren Project is an international, multicentre registry formed to document the main features of primary Sjögren's syndrome at diagnosis, and has highlighted several non-sicca clinical features which do not feature in current classification criteria (Brito Zeron et al, 2015). Geoepidemiology and ethnic variations in expressions are also being explored.

Outcome measures for clinical trials have recently been established. Eular Sjögren's syndrome disease activity index is a clinical index that measures disease activity in primary Sjögren's syndrome. This has been validated and is used

KEY POINTS

- Sjögren's syndrome is a systemic autoimmune disease with a variable presentation.
- Diagnosis of Sjögren's syndrome is aided by American-European Consensus Group criteria, incorporating symptoms, clinical signs, histopathology and autoimmune serology.
- Treatment is generally symptomatic, but systemic immunosuppression is used for significant systemic manifestations.

in most clinical studies and randomized controlled trials (Seror et al, 2015). Eular Sjögren's syndrome patient reported index is a questionnaire designed to assess the severity of patients' symptoms (Seror et al, 2011). Salivary gland histology may also emerge as an outcome measure in clinical trials (Barone et al, 2015).

Histopathology has a growing role in both the diagnosis and prognosis of Sjögren's syndrome. Germinal centre-like structures or a focus score ≥3 may suggest a future high risk for lymphoma development (Theander et al, 2011). Baseline histology also predicts response to rituximab (Delli et al, 2016).

There is emerging evidence for salivary gland ultrasound in the diagnosis of Sjögren's syndrome and its correlation with lip biopsy and other imaging techniques (Astorri et al, 2016). Ultrasound typically shows multiple hypoechoic areas with convex borders. Hyperechoic linear bands, cysts and calcifications may be seen in patients with more advanced disease.

Encouraging results have been seen in an open-label phase II study of belimumab in primary Sjögren's syndrome (Mariette et al, 2013).

Conclusions

Sjögren's syndrome has a wide-ranging clinical spectrum at presentation that includes systemic involvement. It predominantly affects middle-aged women. There are many causes of sicca syndrome and a definite diagnosis of Sjögren's requires established sicca symptoms, objective evidence of dry eyes and mouth, and analytical evidence of autoimmunity. Treatment is mainly symptomatic, and immunosuppression is used for systemic manifestations. Of all autoimmune diseases, Sjögren's syndrome is associated with the highest lifetime risk of developing lymphoma. **BJHM**

Conflict of interest: none.

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