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Sjögren's syndrome in 2013

Key points

- Sjögren's syndrome is an inflammatory autoimmune disease that commonly presents with sicca symptoms but can affect almost any organ and have a major impact on quality of life.
- Severe lower urinary tract symptoms, autonomic dysfunction and obstructive sleep apnoea have recently been recognised as common in primary Sjögren's syndrome.
- Lymphoma is a well-known complication, and regular surveillance is necessary.
- Symptomatic treatment of sicca symptoms and prevention of corneal and periodontal disease are the mainstays of management.
- Hydroxychloroquine may be considered for skin rash, fatigue, arthralgia and myalgia.
- Immunosuppressive agents may be warranted for significant inflammation of vital organs.
- Rituximab shows promise for improving oral dryness, fatigue and vasculitis and is a proven therapy for lymphoma.

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Sjögren's syndrome is an autoimmune disease that commonly causes dry eyes and mouth but can affect almost any organ. Management includes relief of sicca symptoms, monitoring for extraglandular complications and use of immunosuppressive agents when required.

Sjögren's syndrome was first described in 1933 by Henrik Sjögren, a Swedish ophthalmologist. It is a slowly progressive, systemic disease in which an inflammatory autoimmune process affects primarily the exocrine glands. Lymphocytic infiltrates replace functional epithelium, leading to decreased exocrine secretions.[1] The syndrome therefore commonly manifests with sicca symptoms, such as dryness of the eyes and mouth, but can involve almost any organ system.

Sjögren's syndrome must be distinguished from nonautoimmune sicca syndrome (dry mouth and eyes), which is not a systemic disease and does not have extraglandular complications. Sicca symptoms are common in the elderly, occurring in around a quarter of those aged over 65 years.[2] They are usually attributed to factors such as age-related atrophy of exocrine glands and drug side effects. Common drugs that can have sicca side effects are shown in the box on page 27.[3]

Sjögren's syndrome can be classified as primary or as secondary when it is associated with another autoimmune condition. Diseases commonly associated with secondary Sjögren's syndrome include rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis.

EPIDEMIOLOGY

Sjögren's syndrome is more common in women than men, at a ratio of nine to one. Onset is usually in the fourth or fifth decade of life, but it can also affect children and the elderly. The reported prevalence in western countries is between 0.1 and 1%.[4,5]

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PATHOGENESIS

Primary Sjögren's syndrome

The cause of primary Sjögren's syndrome remains unknown but it is postulated to result from the interaction of genetic and environmental factors. Pathogenesis is believed to involve the following steps:

1. An unknown environmental factor acts on a genetically susceptible individual to trigger autoimmunity with autoantibody formation.
2. The autoimmune reaction becomes chronic and is perpetuated by immune mechanisms.
3. Ongoing inflammation with lymphocytic proliferation leads to tissue damage.

Much progress has been made in understanding the immunogenetics of this disease. There is evidence of familial clusters, and family members of patients with Sjögren's syndrome have a higher incidence of abnormal autoimmune serology than age- and sex-matched controls. The disease has been associated with polymorphic major histocompatibility complex (MHC) class II genes, specifically human leucocyte antigen (HLA) DR and DQ alleles.[6] Other genetic risk factors were reported recently; for example, a low copy number of the *FCGR3B* (Fc-γ receptor 3B) gene is a susceptibility factor for primary Sjögren's syndrome, and polymorphisms of the *CTLA4* (cytotoxic T lymphocyte-associated antigen 4) gene appear to influence both susceptibility and certain extraglandular manifestations, especially daytime somnolence.[7,8]

Biopsies show that the salivary gland lesions are composed of CD4+ T lymphocytes in the early stages and later of B lymphocytes. The increased B cell population carries a risk of progression to B cell lymphoma. However, the transition to monoclonal B cell lymphoma is not fully understood, and a chronic autoimmune state is believed to play a role.[9]

The presence of autoantibodies is a hallmark of primary Sjögren's syndrome. Around 70% of patients are positive for antinuclear antibodies (ANA); when these ANA antibodies are characterised, 80% are positive for anti-Ro antibodies and 60% for anti-La antibodies. Ro and La (also known as SSA and SSB, respectively) are nuclear proteins that are involved in ribonucleoprotein structure. The production of anti-Ro and anti-La antibodies is associated with certain HLA haplotypes, particularly HLA-B8-DR3-DQ2. The role of these antibodies in Sjögren's syndrome has not been clear but it was recently discovered that immune complexes containing Ro/RNA and La/RNA are able to activate B cells and dendritic cells and drive immune responses independent of T cell co-stimulation. Genes responsible for regulation of complement activation may also contribute to the autoantibody response in patients with primary Sjögren's syndrome.[10] There is thus a complex interplay between the adaptive and innate branches of the immune system in driving chronic inflammation.

The presence of both anti-Ro and anti-La antibodies together is 90 to 100% specific for Sjögren's syndrome and is associated with younger age at disease onset, increased glandular dysfunction and extraglandular manifestations. In pregnant women, these antibodies also predispose the developing fetus to neonatal lupus and congenital heart block, which complicate 1 to 2% of anti-Ro/anti-La-positive pregnancies.

Up to 60% of patients with primary Sjögren's syndrome are positive for rheumatoid factor, the clinical relevance of which is uncertain. Experimental studies have detected functional autoantibodies that target M3 muscarinic acetylcholine receptors, which may explain the common finding of salivary and lacrimal gland hypofunction in the presence of plentiful residual glandular tissue of normal appearance.[11] These muscarinic receptor autoantibodies have the potential to cause symptoms of autonomic dysfunction (cardiovascular abnormalities, bladder irritability, gastrointestinal disturbances), which are also often seen in primary Sjögren's syndrome.[12]

DRUGS WITH SICCA SIDE EFFECTS[3]

- Opioids
- Tricyclic antidepressants
- Anticholinergic drugs (atropine, scopolamine)
- Sympathomimetic drugs (ephedrine)
- Benzodiazepines
- Selective serotonin reuptake inhibitors
- Phenothiazines
- Antihistamines
- Nicotine
- α_1-Antagonists (terazosin, prazosin)
- α_2-Antagonists (clonidine)
- β-Blockers (atenolol, propranolol)
- Diuretics

Secondary Sjögren's syndrome

Patients with secondary Sjögren's syndrome typically have serum autoantibodies specific to their primary disorder rather than anti-Ro and anti-La antibodies; these include antibodies to cyclic citrullinated peptide (anti-CCP) in rheumatoid arthritis and double-stranded DNA (anti-dsDNA) in systemic lupus erythematosus, and anticentromere or topoisomerase antibodies in systemic sclerosis. However, muscarinic receptor autoantibodies are prevalent in both primary and secondary Sjögren's syndrome, providing a unifying pathogenic link.

CLINICAL FEATURES

The clinical presentation of primary Sjögren's syndrome is variable and the onset can be insidious. The disease usually runs a chronic benign course but the long-term symptoms mean patients often report reduced quality of life, and their functional disability equals that of people with systemic lupus erythematosus.[13]

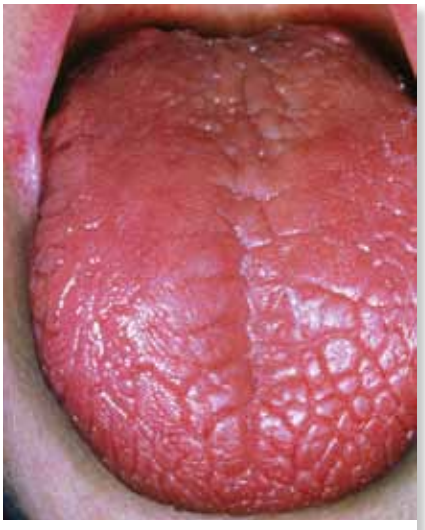


Figure 1. Depapillated red tongue in a patient with Sjögren's syndrome.

Glandular manifestations

Dry eyes and xerostomia (dry mouth) are the most common presenting features, occurring in more than 95% of patients with Sjögren's syndrome. Patients have often had these symptoms for months to years before presentation. Basal tear and saliva production are diminished or absent, although stimulated secretion is often preserved. Diminished tear secretion can lead to keratoconjunctivitis sicca, with symptoms of chronic eye irritation and destruction of the corneal conjunctival epithelium.

Patients presenting with keratoconjunctivitis sicca frequently complain of eye itching and grittiness, a burning or scratchy sensation under the eyelids, eye redness and photosensitivity. Those with xerostomia report difficulty in chewing and swallowing dry food, difficulty in speaking continuously and a burning sensation in the mouth; they are at increased risk of periodontal disease and dental caries. Physical signs include a dry, erythematous mucosa, a lobulated or depapillated red tongue, gum recession with cervical tooth erosions, and angular cheilitis (Figure 1).

Unilateral or bilateral enlargement of the parotid or other major salivary glands can be detected in up to 60% of patients with Sjögren's syndrome. Gland enlargement (parotitis) can be episodic or persistent. A rapidly enlarging gland may herald the emergence of malignant B cell lymphoma, and fine needle aspiration or biopsy of the gland should be considered. Fever, malaise and anorexia together with expression of purulent saliva indicate a bacterial infection, a known complication of chronic parotitis.

Dryness of mucosal surfaces can cause a hoarse voice, recurrent bronchitis and pneumonitis. Reduced vaginal secretions, skin dryness, loss of pancreatic function and hypochlorhydria are also seen.

Extraglandular manifestations

Extraglandular manifestations of primary Sjögren's syndrome include general constitutional symptoms such as fatigue, low-grade fever, myalgias and arthralgias, as well as organ-specific complications.

Fatigue occurs in up to 70% of patients; the mechanism is poorly understood but it is likely due to a combination of factors, including cytokine-mediated effects on the central nervous system and sleep interruption caused by musculoskeletal pain, the need to drink water overnight to relieve a dry mouth and the need to get up to urinate. Daytime somnolence is also increased.[14] A recent study suggested that obstructive sleep apnoea is more common in patients with primary Sjögren's syndrome; this may be related to dryness of the upper airways which has been shown to increase surface tension in the airways, potentially increasing their collapsibility.[15,16] As fatigue and daytime somnolence caused by obstructive sleep apnoea can be reduced by continuous positive airway pressure (CPAP) treatment in selected patients, it is important to exclude this condition in patients with these symptoms.

Organ-specific complications can involve virtually any organ system (Table). Up to 37% of patients report Raynaud's phenomenon. Patients can develop chronic cough and dyspnoea from obstructive lung disease (chronic bronchitis or bronchiectasis) and, less commonly, interstitial lung disease. Patients are also at increased risk of renal complications such as renal tubular acidosis, recurrent renal calculi and glomerulonephritis; around 40% report lower urinary tract symptoms (frequency, urgency, nocturia).

There is also an association between primary Sjögren's syndrome and autoimmune conditions of the hepatobiliary system (primary biliary cirrhosis, autoimmune hepatitis) and rarely, recurrent pancreatitis. Autoimmune dysfunction of the autonomic nervous system and thyroid gland, nonerosive polyarthritis and cutaneous vasculitis are also common.[17] Clinical studies using MRI scans have demonstrated the presence of central nervous system white matter lesions in approximately half of patients with Sjögren's syndrome, which may account for reports of subtle cognitive impairment.[18]

Lymphoproliferative disease

The association between Sjögren's syndrome and lymphoma is well documented. Patients with Sjögren's syndrome have a 44-fold relative risk of developing lymphoma compared with age and sex-matched people in the general population.[19] Even when compared with patients with other autoimmune diseases, such as systemic lupus erythematosus or rheumatoid arthritis (also known to increase the risk of lymphoma), patients with primary Sjögren's syndrome are at greater risk of this complication.

The prevalence of non-Hodgkin's lymphoma in patients with Sjögren's syndrome is estimated at 4.3%,[19] with a median age at diagnosis of 58 years. In a recent large cohort study of 244 patients with primary Sjögren's syndrome, 4.5% developed non-Hodgkin's lymphoma over a median follow-up period of 8 years, and the most common forms were diffuse large B-cell and mucosa-associated lymphoid tissue (MALT) lymphomas.[20] Clinicoserological predictive factors for developing lymphoma early after diagnosis of primary Sjögren's syndrome included purpura,

TABLE. ORGAN-SPECIFIC EXTRAGLANDULAR MANIFESTATIONS OF SJÖGREN'S SYNDROME*[3]

Clinical presentation	Cases	Clinical presentation	Cases
Skin		**Liver/pancreas**	
Purpura/cutaneous vasculitis (usually with cryoglobulinaemia)	10–15%	Primary biliary cirrhosis	3–8%
		Autoimmune hepatitis	< 5%
Annular erythema (nonscarring wide erythematous plaques)	5–10%	Recurrent pancreatitis	< 5%
		Peripheral nervous system	
Joints		Mixed polyneuropathy	5–10%
Nonerosive symmetrical arthritis	15–30%	Pure sensory neuropathy	5%
Lungs		Mononeuritis multiplex	5%
Chronic obstructive lung disease	10%	Small fibre neuropathy	< 5%
Bronchiectasis	8%	Autonomic dysfunction (usually mild)	55%[12,17]
Interstitial lung disease	5%	**Central nervous system**	
Bronchiolitis obliterans	< 5%	White matter lesions (multiple sclerosis-like)	50–55%[18]
Cardiovascular		Cranial nerve involvement (V, VII and VIII)	7%
Raynaud's phenomenon	18–37%	Myelitis	< 5%
Pericarditis	< 5%	**Thyroid**	
Renal		Autoimmune thyroiditis	14–33%
Renal tubular acidosis	11%	**Haematological**	
Glomerulonephritis	< 5%	Anaemia of chronic disease	25%
Interstitial cystitis	< 5%	Autoimmune haemolytic anaemia	< 5%
Recurrent renal calculi	< 5%	Severe thrombocytopenia	< 5%
Lower urinary tract symptoms†	40%[14]	B cell lymphoma	5%

* Adapted from Ramos-Casals et al. BMJ 2012; 344: e3821.[3] † Including frequency, urgency, nocturia.

parotidomegaly, anaemia, raised gamma globulin levels and low levels of white blood cells, lymphocytes and complement C3 and C4, but only low lymphocyte and complement levels were independent risk factors.[20]

DIAGNOSIS AND INVESTIGATION

Criteria for diagnosis

An American–European Consensus Group (AECG) on Sjögren's syndrome has developed a set of criteria that is used primarily for entry to clinical research studies but has also been adopted for diagnosis.[21] These criteria require objective evidence of autoimmunity for a definite diagnosis of Sjögren's syndrome – either anti-Ro or anti-La autoantibodies or a labial biopsy demonstrating focal sialoadenitis (see the box on page 32).[21] A six-item questionnaire was developed to aid in initial screening for sicca symptoms (items I and II in the box), but patients with no sicca symptoms can be diagnosed with Sjögren's syndrome if they meet three out of four objective criteria (items III to VI). The sensitivity and specificity of the AECG criteria for diagnosis of primary Sjögren's syndrome are 97% and 49%, respectively.

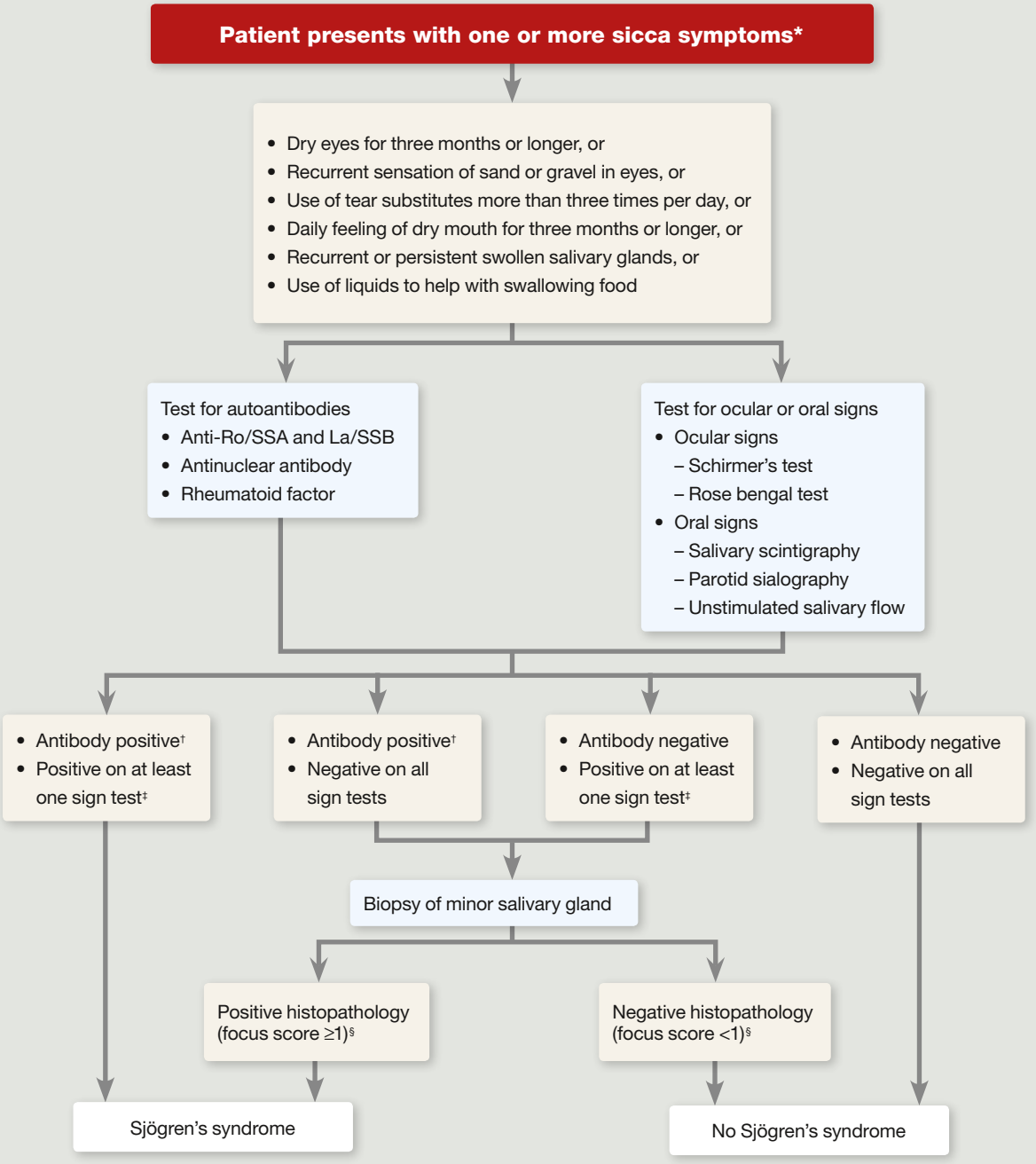
A diagnostic algorithm for Sjögren's syndrome that uses these criteria and can be applied in a clinical setting is shown in the flowchart on page 31.[1]

More recently, a Sjögren's international collaborative group has proposed new criteria to improve specificity for clinical research purposes. These are based entirely on objective tests (serology and ocular and salivary tests) and do not include subjective reporting of ocular or oral symptoms.[22]

Diagnostic investigations

Specific ocular and salivary gland testing, including imaging studies, may help support the diagnosis of Sjögren's syndrome, but a positive result on salivary gland biopsy remains the 'gold standard' for confirming the diagnosis and is necessary in patients who are negative for anti-Ro and anti-La antibodies. Salivary gland biopsy is best performed by labial biopsy of the minor salivary glands, which is a simple procedure that can be performed

DIAGNOSTIC ALGORITHM FOR SJÖGREN'S SYNDROME[1]



* Excludes patients with hepatitis C, HIV infection, sarcoidosis, graft versus host disease, pre-existing lymphoma or previous head or neck irradiation and those using anticholinergic drugs.
† Antibody positive: positive for anti-Ro or anti-La antibodies or both.
‡ Positive (abnormal) results for oral or ocular tests: Schirmer's test, tear wetting of 5 mm or less in five minutes; rose bengal test, score of 4 or more according to van Bijsterveld's scoring system; unstimulated salivary flow, volume of 1.5 mL or less in 15 minutes.
§ Histopathology focus score = number of foci of 50 or more mononuclear cells per 4 mm^2.
Adapted from Tzioufas et al (2011).[1]

AMERICAN–EUROPEAN CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME (2002)[21]

Criteria for primary Sjögren's syndrome

In patients who have no disease potentially associated with Sjögren's syndrome, primary Sjögren's syndrome may be defined as follows:

- the presence of any four of the six items below, as long as either item IV (histopathology) or VI (serology) is positive or
- the presence of any three of the four objective criteria below (items III to VI).

Criteria for secondary Sjögren's syndrome

In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any two from among items III to V may be considered indicative of secondary Sjögren's syndrome.

Exclusion criteria

- Past head and neck radiation treatment
- Hepatitis C infection
- AIDS
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs (since a time shorter than four times the half-life of the drug)

Item I. 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 a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes more than three times a day?

Item II. Oral symptoms

A positive response to at least one of the following questions:

- Have you had a daily feeling of dry mouth for more than three months?
- Have you had recurrently or persistently swollen salivary glands as an adult?
- Do you frequently drink liquids to aid in swallowing dry food?

Item III. Ocular signs

Objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

- Schirmer's test, performed without anaesthesia (positive result: tear wetting of 5 mm or less in five minutes)
- rose bengal or other ocular dye test (positive result: score of 4 or more according to van Bijsterveld's scoring system)

Item IV. Histopathology

In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist as a focus score of 1 or more, with the score defined as the number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.

Item V. Salivary gland involvement

Objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

- unstimulated whole salivary flow (positive result: volume of 1.5 mL or less in 15 minutes)
- parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
- salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

Item VI. Autoantibodies

Presence in the serum of autoantibodies to Ro(SSA) or La(SSB) antigens.

under local anaesthesia by a dentist trained in the appropriate collection procedure (Figures 2a and b).[23] As with all histopathology, it is reader dependent and best performed by a histopathologist with a specific interest in Sjögren's syndrome. It is useful to provide a completed pathology request form with the dentist's referral, requesting 'H&E: please report the focus score (number of foci of 50 or more mononuclear cells per 4 mm^2)'.

Schirmer's test for dry eyes is easily performed in an outpatient environment; a strip of sterile filter paper is placed overhanging the lateral third of the lower eyelid of each eye and left for five minutes (Figure 3a). Normal tear production usually results in wetting of 15 mm or more of the strip, with 5 mm or less considered positive (abnormal). Alternative tests to demonstrate objective ocular dryness include the rose bengal test, lissamine green test and tear break-up time, which require a slit lamp and are usually performed by an ophthalmologist.

The simplest way to demonstrate objective oral dryness is estimation of unstimulated whole salivary production by asking the patient to collect saliva in a calibrated tube for 15 minutes (Figure 3b). A volume of 1.5 mL or less is considered abnormal.

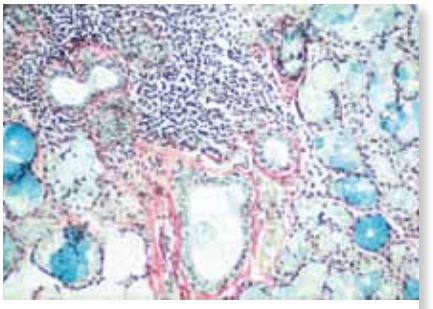
Radionuclear sialometry is not commonly used and is not standardised in most Australian centres. Sialography, performed after cannulation of the parotid duct and injection of radiocontrast material, is invasive, often painful, and not required for routine diagnosis.

Monitoring for extraglandular complications

Routine laboratory testing may be performed initially every six to 12 months to monitor for extraglandular complications and then less frequently depending on clinical status. Several nonspecific abnormalities can be revealed. A quarter of patients with primary Sjögren's syndrome have anaemia of chronic disease, and they often have an elevated erythrocyte sedimentation rate (80 to 90%). This finding is due to diffuse polyclonal hypergammaglobulinaemia associated with B cell proliferation. However, if there is any suspicion raised by history and physical examination (such as unexplained weight loss, palpable organomegaly and/or palpable lymph nodes) or a rising globulin count then the possibility of a lymphoma should be investigated. This should include serum electrophoresis to look for monoclonal gammopathy and CT scan of the neck, chest, abdomen and pelvis.

C-reactive protein levels are usually within normal limits. Raised levels of gamma glutamyl transferase or liver transaminases may indicate primary biliary cirrhosis or autoimmune hepatitis, respectively. Abnormal thyroid function (frequently hypothyroidism), together with positive thyroid autoantibodies are found in those with autoimmune thyroiditis. Imaging studies are useful depending on the presenting complaint; for example, chest x-ray, high resolution CT scan and lung function tests could be useful for dyspnoea and findings of crepitations on physical examination.

Urinary tract symptoms warrant urinalysis to exclude infectious causes. The presence of abnormal red blood cells and casts suggests upper urinary tract complications. Patients with low plasma bicarbonate and potassium levels should be investigated for possible distal renal tubular acidosis; these patients will have normal anion gap metabolic acidosis with a urine pH >5.5 caused by a defect in distal urinary acidification.



Figures 2a and b. a (left). Site of labial biopsy. b (right). A biopsy specimen positive for Sjögren's syndrome, showing focal lymphocytic sialoadenitis. Aggregates of lymphocytes are visible in a periductal distribution (haematoxylin and eosin stain).

Serological autoimmune abnormalities as discussed previously include positive ANA, anti-Ro and anti-La antibodies, and rheumatoid factor. These generally do not alter over time.

TREATMENT

Treatment of sicca symptoms

Initial treatment is aimed at alleviating the discomfort caused by dry eyes and dry mouth, but effective relief is often frustratingly difficult. Most patients require regular follow up with an ophthalmologist to ensure timely screening for corneal damage and specialised care if keratoconjunctivitis sicca becomes severe.

Dry eyes

Treatments for dry eyes include the use of artificial tears and lubricating eye ointments, which contain ingredients such as hypromellose, sodium hyaluronate and liquid paraffin and are readily available over the counter. Artificial tears may be used several times a day, or more often in low-humidity environments such as aeroplanes. Ointments stay longer in the eye than artificial tears but may cause temporary blurring of vision and therefore are preferably used at bedtime. Preservative-free options are preferred for long-term use, to minimise irritation and the development of sensitivity to preservatives. Some ophthalmologists provide ocular lubricants based on autologous serum, but care is needed to avoid bacterial contamination.

Potentially drying environments should be avoided as far as possible, including air-conditioned rooms, smoke, wind and low humidity. Patients often find wraparound sunglasses or modified goggles help to minimise eye irritation, by limiting air blowing onto the eyes. Room humidifiers or even strategically placed bowls of water can also reduce symptoms of ocular and upper respiratory dryness.

In more severe cases, a procedure to occlude the lacrimal punctum and hence

Figures 3a and b. a (left). Schirmer's test for eye dryness. b (right). Estimation of whole unstimulated salivary production.

inhibit tear drainage from the eye, performed by an ophthalmologist, can be very effective. Topical cyclosporin is used in the USA to increase tear flow, with some controlled evidence to support its use, but it is not approved for this indication by the TGA in Australia.[24]

Mouth dryness

Patients with Sjögren's syndrome require regular dental follow up to maintain overall dental health. Common complications resulting from poor saliva production include gum recession, gingival disease, accelerated dental caries, halitosis, oral thrush and dysphagia.

Factors that aggravate dry mouth symptoms, such as alcohol, caffeine and smoking, should be avoided. Concomitant sinusitis or rhinitis should be treated as they can lead to mouth breathing and further drying of the oral cavity. It is best to avoid use of antihistamines in allergic rhinosinusitis and conjunctivitis, and to consider corticosteroid or saline nasal sprays.

Treatment of dry mouth aims to maintain lubrication with a saliva substitute or medicated gel and/or stimulating salivary production. Patients should also be encouraged to drink, sip or gargle frequently with water. Most patients find some benefit from sucking on sugar-free lozenges or chewing sugar-free gum to stimulate salivary flow.

Pilocarpine, a muscarinic receptor agonist, has shown effectiveness in reducing symptoms of xerostomia, but evidence of its effect on salivary secretion rate is still lacking.[25,26] It can cause uncomfortable side effects, such as nausea, flushing, sweating, and urinary frequency, and should be used with caution in patients with cardiac disease or asthma because of the risks of bradycardia and bronchospasm, respectively. Pilocarpine should be begun at a low dose such as 5 mg taken orally twice a day, with titration upwards as needed and tolerated, to a maximum of 30 mg daily in three or four divided doses. As pilocarpine is not marketed for Sjögren's syndrome in Australia, this use is off licence. It needs to be formulated by a compounding pharmacist or diluted from pilocarpine eye drops (off-label use).

Cevimeline is a more selective M3 muscarinic receptor agonist licensed in the USA for treatment of mouth dryness in Sjögren's syndrome but is not available in Australia.

Other sicca symptoms

Vaginal and nasal lubricants and skin moisturisers can be used as required.

Treatment of extraglandular manifestations

Systemic treatment is usually considered when extraglandular manifestations become clinically relevant. Fatigue can be debilitating and reduce patients' quality of life and ability to function, as can non-specific arthralgia and myalgia. The general approach after excluding comorbidities such as obstructive sleep apnoea and gastro-oesophageal reflux disease is to recommend lifestyle modifications, regular exercise, physiotherapy and a regular sleep pattern. Paracetamol and NSAIDs are recommended for simple analgesia, but use of NSAIDs may be limited by dysphagia, poor oesophageal motility and gastric reflux disease.

Hydroxychloroquine has shown some efficacy in relieving symptoms of fatigue, arthralgia and myalgia, as well as subacute cutaneous lupus skin lesions.[27] Patients taking long-term hydroxychloroquine need regular eye checks (every 12 months or as directed by their ophthalmologist) to detect the rare complication of retinopathy at an early and reversible stage.

Patients with Sjögren's syndrome complicated by distal renal tubular acidosis are generally treated with sodium bicarbonate, with the aim of correcting the metabolic acidosis and maintaining a relatively normal serum bicarbonate level.

There is no convincing evidence supporting the use of corticosteroids (prednisolone) in uncomplicated Sjögren's syndrome, but it may be necessary for patients who develop vasculitis, pneumonitis, neuropathy or nephritis. Other immunosuppressives investigated include methotrexate and azathioprine, which have unconvincing results in primary Sjögren's syndrome.[28,29] Methotrexate is used primarily if the patient has features of a concomitant inflammatory arthritis. When considering the use of immunosuppressives, referral to a rheumatologist would be appropriate.

Recent controlled studies have attempted to assess the efficacy of biologic disease-modifying antirheumatic drugs for arthralgia and severe sicca symptoms in primary Sjögren's syndrome. Results so far have been disappointing for anti-tumour necrosis factor (anti-TNF) agents, with both infliximab and etanercept trials failing to achieve primary outcomes.[24] Early trials of the anti-CD20 agent rituximab have shown promise in improving salivary flow rate and fatigue.[30,31] Rituximab has an established role in the treatment of B-cell lymphoma, and has been associated with improvement in vasculitic peripheral neuropathy associated with Sjögren's syndrome.[32]

In rare life-threatening situations – usually rapidly progressive extraglandular diseases (glomerulonephritis, interstitial lung disease, myositis, myelitis) or systemic vasculitis – cyclophosphamide and methylprednisolone, rituximab or plasma exchange may be required.

PROGNOSIS

Patients with Sjögren's syndrome have an all-cause mortality rate similar to that of the general population. However, they are at increased risk of dying from lymphoma, with a cause-specific standardised mortality ratio of 7.89, corresponding to 2.53 excess deaths per 1000 person-years at risk.[33]

CONCLUSION

Sjögren's syndrome is a slowly progressive, inflammatory autoimmune condition that usually presents with sicca symptoms and may cause significant morbidity and poor quality of life. Management includes lifestyle modification, topical lubricants, analgesics and frequently hydroxychloroquine.

Extraglandular manifestations, including non-Hodgkin's lymphoma, are relatively common and regular surveillance is necessary. Immunosuppressive agents may be indicated in the management of Sjögren's syndrome complicated by significant inflammation of vital organs. MT

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