

# Beyond sicca symptoms

## Diagnosis and management of Sjögren disease

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Sjögren disease commonly causes dry eyes and dry mouth but may also involve the joints, lungs, kidneys, nervous system and other organs. Diagnosis can be challenging because sicca symptoms are common and anti-Ro/Sjögren syndrome antigen A antibodies are absent in about 20% of patients. Management remains largely symptomatic and multidisciplinary, although novel biologic therapies are being investigated.

**S**jögren disease is a systemic autoimmune connective tissue disease that may occur as primary Sjögren disease or Sjögren disease in association with other connective tissue diseases (known as associated Sjögren disease). Although Sjögren disease is well known for causing dry eyes and dry mouth, systemic involvement occurs in about 70% of patients and can include serious manifestations such as interstitial



### KEY POINTS

- Sjögren disease may occur as a primary disease or in association with another systemic autoimmune disease.
- Systemic involvement occurs in about 70% of patients and may include inflammatory arthritis, interstitial lung disease, renal disease, vasculitis, peripheral neuropathy and lymphoma.
- Persistent sicca symptoms, parotid enlargement, unexplained dental caries or suggestive systemic features should prompt investigation for Sjögren disease.
- The absence of anti-Ro/Sjögren syndrome antigen A antibodies does not exclude the diagnosis; objective tests of ocular and oral dryness and salivary gland biopsy may be required.
- Management is multidisciplinary and focuses on relieving sicca symptoms, treating systemic manifestations, monitoring for complications and supporting quality of life.

lung disease, renal involvement, lymphoma and pregnancy complications.<sup>1</sup> There is growing recognition of distinct Sjögren disease phenotypes, potentially influenced by ethnicity, sex and geographical location.<sup>2</sup> Recent evidence also indicates that patients with Sjögren disease have a twofold higher risk of mortality than the general population.<sup>3</sup>

Importantly, Sjögren disease can substantially affect quality of life because of symptom burden, social isolation and functional impairment.<sup>4</sup> Although Sjögren disease is the second most common autoimmune rheumatic disease and several randomised clinical trials have examined potential therapies, management remains symptomatic, with no approved therapies to modify disease progression or complications.<sup>5</sup> This article provides an overview of the diagnosis and management of Sjögren disease, including its systemic manifestations and pregnancy complications.

### Change in nomenclature

The nomenclature for Sjögren disease has recently changed from Sjögren (or Sjögren's) syndrome to Sjögren (or Sjögren's) disease.

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Australian  
Rheumatology  
Association

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This terminology was endorsed after consensus was reached through a Delphi process involving 79 professionals and 1431 patients from 34 countries. It reflects recognition that Sjögren disease is a distinct autoimmune disease characterised by autoantibodies, glandular histopathology and a specific pattern of systemic involvement.<sup>6</sup> Patients emphasised that the term 'syndrome' can be counterproductive because it implies that Sjögren disease is a loose collection of ill-defined or 'nuisance' symptoms (predominantly sicca symptoms), rather than a disease associated with serious morbidity and, in some patients, increased mortality.

The Delphi process also reached clear consensus on replacing the term 'secondary' with 'associated' when classifying Sjögren disease that co-occurs with another systemic autoimmune disease. However, no clear consensus was reached on the value or utility in distinguishing primary from associated Sjögren disease. Currently, 'primary' is used mainly in scientific literature to define study populations.

## Epidemiology

International estimates of the prevalence of Sjögren disease range from 0.01 to 0.33%, with the upper estimate equivalent to about one in 300 people.<sup>7</sup> The annual incidence is estimated at one to 10 per 100,000 person-years, comparable with that of systemic lupus erythematosus (SLE; 5.14 per 100,000 person-years) and systemic sclerosis (1.4 per 100,000 person-years).<sup>8-10</sup> Although Sjögren disease predominantly affects women and is usually diagnosed in their fifties, the female-to-male ratio varies by ethnicity. In a large international retrospective cohort study (N = 10,007), the highest and lowest ratios were reported among people of Asian ancestry (27:1) and African American ancestry (7:1), respectively.<sup>2</sup>

Compared with women, men with Sjögren disease have higher rates of systemic involvement and more often have peripheral and central nervous system involvement and lymphadenopathy at

disease onset.<sup>2,11</sup> Our understanding of the epidemiology of paediatric Sjögren disease is also expanding rapidly. A large multinational cohort study found that paediatric Sjögren disease accounted for 1.3% (N = 158) of all Sjögren disease cases, although its precise incidence and prevalence remain unknown.<sup>12</sup>

## Pathophysiology

Sjögren disease is characterised by lymphocytic infiltration of the exocrine glands, particularly the salivary and lacrimal glands, resulting in glandular dysfunction and destruction. In genetically susceptible people, an infectious trigger, such as Epstein-Barr virus, cytomegalovirus or coxsackie virus, together with hormonal factors, such as declining oestrogen levels during menopause, is thought to cause aberrant immune activation. This results in autoantibody production, including anti-Ro/Sjögren syndrome antigen A (SSA) and anti-La/Sjögren syndrome antigen B (SSB) antibodies, and perpetuation of the inflammatory response through T- and B-cell infiltration of the glands.<sup>13</sup>

## Presentation and diagnosis

Diagnosing Sjögren disease can be challenging because the hallmark sicca symptoms of dry eyes and dry mouth are common in the general population. Dry mouth affects 13.2% of Australian adults, increasing to 24.5% among those older than 75 years because of salivary gland atrophy, whereas dry eye symptoms affect 13% of Australian adults.<sup>14,15</sup> Important differential diagnoses for sicca symptoms are summarised in Box 1. Diagnostic delays of up to six years have been reported in people with Sjögren disease. Longer delays are associated with poorer health outcomes, including greater vaginal dryness, more gastrointestinal symptoms, breathlessness and skin lesions, as well as greater use of health services.<sup>16</sup>

## Symptoms

The characteristic keratoconjunctivitis sicca of Sjögren disease may cause burning,

### 1. DIFFERENTIAL DIAGNOSES FOR SICCA SYMPTOMS IN ADULTS

- Medications:
  - anticholinergic drugs
  - antihistamines
  - opioids
  - antidepressants
- Low-humidity environments
- Thyroid disorders:
  - Hashimoto's thyroiditis
  - Graves' disease
- Diabetes mellitus
- Graft-versus-host disease
- Infiltrative disorders:
  - sarcoidosis
  - amyloidosis
  - immunoglobulin G4-related disease
- Infections:
  - tuberculosis
  - hepatitis C
  - HIV
- Irradiation:
  - head and neck irradiation
  - radioactive iodine therapy
- Trauma:
  - salivary gland injury causing dry mouth
  - cataract surgery or laser eye surgery causing dry eyes
- Age-related salivary gland atrophy
- Psychological conditions:
  - anxiety or depression
  - post-traumatic stress disorder

itching or a gritty sensation in the eyes. Xerostomia may cause oral dryness, oral burning, altered taste or difficulty swallowing, requiring frequent sips of water. Women with urogynaecological dryness may report dyspareunia.

Systemic, or extraglandular, involvement is also common and may include inflammatory arthritis, cutaneous vasculitis, interstitial lung disease or peripheral neuropathy, even in the absence of sicca symptoms. Overwhelming fatigue is also common.<sup>17</sup> Sjögren disease may also co-exist with other autoimmune rheumatic disorders, including SLE, rheumatoid arthritis, juvenile idiopathic arthritis and systemic sclerosis. The glandular and extraglandular manifestations of Sjögren

## 2. GLANDULAR AND EXTRAGLANDULAR MANIFESTATIONS OF SJÖGREN DISEASE

### Glandular

- Xerostomia (dry mouth)
- Keratoconjunctivitis sicca (dry eyes)
- Parotid and submandibular gland enlargement
- Vaginal dryness with dyspareunia, urinary urgency and recurrent urinary tract infections
- Dental caries

### Extraglandular

- General:
  - fatigue
  - unexplained fever
  - sleep disturbance
  - unintended weight loss
- Musculoskeletal:
  - inflammatory arthralgia with early-morning stiffness, with or without synovitis
  - myalgias, or, less commonly, myositis
- Vascular:
  - Raynaud's phenomenon
  - hypergammaglobulinaemic, leukocytoclastic or cryoglobulinaemic vasculitis
- Respiratory:
  - chronic obstructive lung disease
  - bronchiectasis
  - interstitial lung disease
- Renal:
  - type 1 renal tubular acidosis, with or without nephrocalcinosis
  - interstitial nephritis
  - glomerulonephritis
  - interstitial cystitis
- Gastrointestinal:
  - oesophageal dysfunction
  - pancreatic dysfunction and pancreatitis
  - atrophic gastritis
- Neurological:
  - transverse myelitis
  - peripheral neuropathy
  - cranial nerve involvement, including the trigeminal, facial and vestibulocochlear nerves
  - multiple sclerosis-like cerebral lesions
  - cognitive dysfunction ('brain fog')
- Skin:
  - palpable purpura associated with vasculitis
  - erythema multiforme
  - subacute cutaneous lupus erythematosus
  - dry skin and pruritus
- Haematological:
  - autoimmune haemolytic anaemia
  - thrombocytopenia
  - neutropenia
  - lymphopenia
  - lymphadenopathy
  - lymphoma
- Pregnancy:
  - congenital heart block
  - other manifestations of neonatal lupus erythematosus, including rash, cytopenias and hepatic involvement

## 3. PAEDIATRIC SJÖGREN DISEASE: KEY POINTS

- Rare, accounting for 1.3% of all cases of Sjögren disease, with a female-to-male ratio of 8:1<sup>12</sup>
- Sicca symptoms are initially less common, but may develop over time<sup>18</sup>
- Serious complications, including lymphoma, may occur<sup>19</sup>
- Presents with recurrent parotid swelling, arthralgia, fatigue and systemic features<sup>20</sup>
- Early diagnosis and intervention may modify the disease course<sup>20</sup>

interstitial lung disease

- a palpable purpuric rash on the lower legs
- lymphadenopathy
- peripheral neuropathy, which may manifest as muscle weakness, reduced reflexes and changes in touch, temperature or pain sensation.

Signs of associated autoimmune rheumatic conditions, such as rheumatoid arthritis, SLE or systemic sclerosis, may also be present. Osteoarthritis, which is common in this demographic, may coexist but is generally unrelated. Paediatric Sjögren disease may present with prominent parotid enlargement, lymphadenopathy and fever on examination.<sup>20</sup>

### Severe manifestations

Non-Hodgkin's lymphoma is a significant and severe manifestation of Sjögren disease. It is usually mucosa-associated lymphoid tissue lymphoma, but may also be diffuse large B-cell lymphoma or follicular lymphoma. The lifetime risk is 5 to 10%, and the risk may be up to 48 times that in the general population. This is substantially greater than the 2.7-fold and 2.46-fold increases in lymphoma risk reported in patients with SLE and rheumatoid arthritis, respectively.<sup>21-23</sup>

Lymphoma may present as persistent, firm parotid gland enlargement, sometimes with associated facial nerve palsy.

disease are summarised in Box 2.

Paediatric Sjögren disease typically presents with recurrent parotitis, including parotid swelling and pain, and systemic features such as unexplained fever, chronic fatigue and lymphadenopathy (Box 3).<sup>12,18-20</sup> Sicca symptoms are less prominent in children, adolescents and young adults, which may reflect their greater lacrimal and salivary gland reserve. However, dryness may become more clinically significant over the course of the disease.<sup>18</sup>

### Physical examination

Physical examination may reveal salivary gland enlargement, particularly of the

parotid glands; a hyperlobulated tongue with loss of the filiform papillae; and an absence of salivary pooling beneath the tongue. Consequences of xerostomia include oral candidiasis, gum recession and dental caries. Enlarged lacrimal glands should prompt consideration of an alternative diagnosis, such as immunoglobulin G4-related disease or lymphoma, as it may be due to other causes. Typical physical examination findings in Sjögren disease are shown in Figures 1a to 1f.

Additional signs may include:

- swollen and tender joints, typically in the hands and wrists
- fine bibasal crepitations on lung auscultation, reflecting



**Figures 1a to f.** Typical physical examination findings in Sjögren disease: (a, top left) parotid swelling; (b, top centre) parotitis; (c, top right) dry, fissured tongue; (d, bottom left) marked gum recession and dental caries; (e, bottom centre) right eye with a para-central corneal ulcer and diffuse keratoconjunctivitis; and (f, bottom right) palpable purpuric rash of the lower leg.

Images courtesy of the authors, except Figure 1e, which is reproduced under a Creative Commons Attribution 4.0 International License from Mtalai N, Ettourni S, El Hadi K, et al. *Eur J Med Health Sci* 2024; 6: 32-34. Images published with patient consent.

This presentation warrants further investigation with imaging, such as ultrasound, CT, MRI or fluorodeoxyglucose positron emission tomography, and gland biopsy. Vasculitis, including cryoglobulinaemic vasculitis, may present with purpuric skin lesions, ischaemic skin ulceration or peripheral neuropathy, or, more rarely, life-threatening renal, gastrointestinal, pulmonary or cerebral involvement. Long disease duration is the main risk factor for vasculitis.<sup>24</sup>

Mortality in Sjögren disease is primarily caused by infection, cardiovascular disease and malignancy, including solid-organ malignancies and lymphoma, particularly in patients with high systemic disease burden. There is, however, a paucity of data in the Australian context.<sup>3</sup>

Pregnancy complications associated

with Sjögren disease include higher rates of miscarriage, preterm birth, low birth-weight and cardiac abnormalities.<sup>25,26</sup> Sjögren disease is also associated with neonatal lupus erythematosus and congenital heart block because of the transplacental transfer of maternal anti-Ro/SSA antibodies. Concurrent anti-La/SSB antibodies further increase fetal risk. These autoantibodies may cause cardiac, cutaneous, haematological or hepatic manifestations in the neonate.<sup>27</sup>

Congenital heart block is usually detected in utero between 18 and 24 weeks' gestation and presents as fetal bradycardia. The live birth rate in complete heart block is 81%.<sup>28</sup> Pregnancies in women with these autoantibodies are high risk, even when a connective tissue disease has not yet been diagnosed, and about 2% are affected by

congenital heart block. If a previous pregnancy resulted in an infant with cutaneous or cardiac neonatal lupus erythematosus, the risk of recurrence increases to 18%.<sup>29</sup>

## Diagnosis

Sjögren disease should be suspected in patients with persistent sicca symptoms for more than three months, parotid gland enlargement, significant unexplained dental caries or systemic symptoms such as inflammatory arthritis, cutaneous vasculitis, interstitial lung disease or peripheral neuropathy. Anti-Ro60/SSA (also known as TROVE2) antibodies or anti-Ro52/SSA (also known as TRIM21) antibodies, or both, are usually present; however, about 20% of patients with Sjögren disease lack these autoantibodies, so their absence does not exclude the diagnosis.<sup>30-32</sup> The

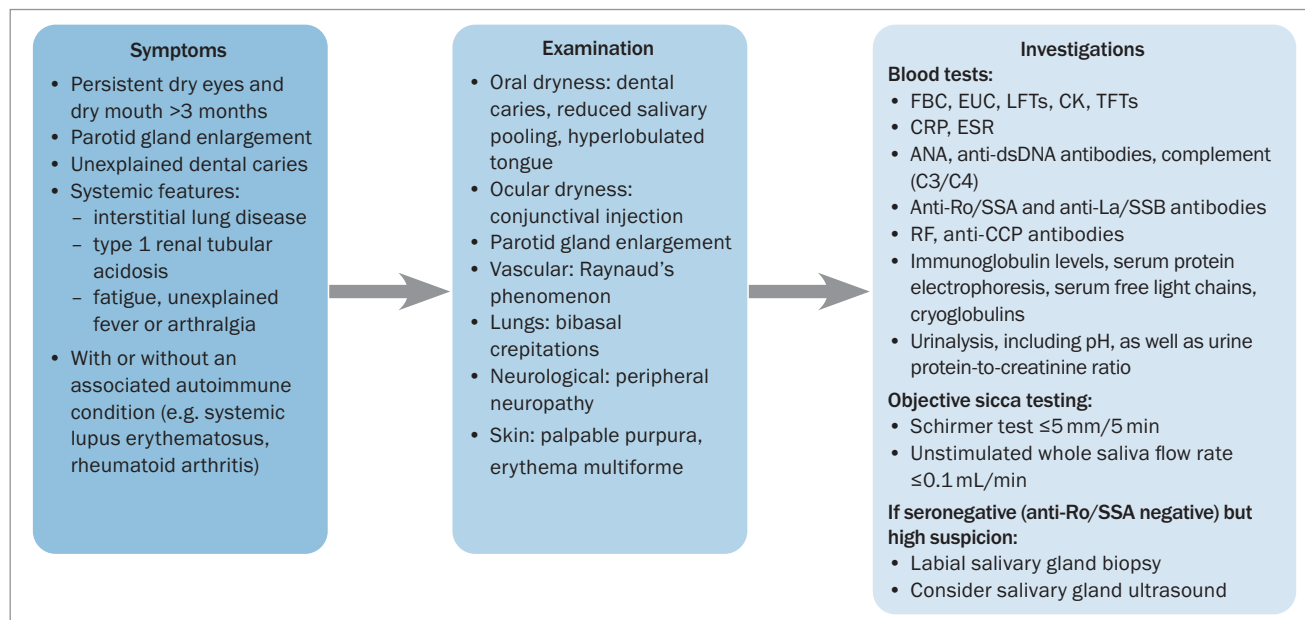


**Figure 2.** Diagnostic approach to suspected Sjögren disease.

Abbreviations: ANA = antinuclear antibody; anti-CCP = anticyclic citrullinated peptide; CK = creatine kinase; CRP = C-reactive protein; dsDNA = double-stranded DNA; ESR = erythrocyte sedimentation rate; EUC = electrolytes, urea and creatinine; FBC = full blood count; LFTs = liver function tests; RF = rheumatoid factor; SSA = Sjögren syndrome antigen A; SSB = Sjögren syndrome antigen B; TFT = thyroid function test.

diagnostic approach to suspected Sjögren disease is outlined in Figure 2.

### Classification criteria

The 2016 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR-EULAR) classification criteria for primary Sjögren disease are generally used in clinical practice because no diagnostic criteria are available (Box 4).<sup>33</sup> The criteria require serum anti-Ro/SSA antibodies or focal sialadenitis on salivary gland biopsy, or both, which provide key evidence of autoimmune causation. They apply to patients with suspected Sjögren disease because of sicca symptoms or suggestive systemic features, including those who do not report sicca symptoms. A score of four points or more is required to confirm the diagnosis of primary Sjögren disease.

### Objective assessment of sicca symptoms

Subjective sicca symptoms correlate poorly with objective evidence of oral or ocular dryness; therefore only objective measures of sicca are scored in the ACR-EULAR

criteria. Ocular dryness can be demonstrated by a positive Schirmer test, which can be performed in the consulting room, or by ocular surface staining, which requires slit-lamp examination. Oral dryness is assessed objectively by measuring the rate of unstimulated salivary flow. The patient collects saliva in a cup or tube over five to 15 minutes; the volume is then measured using a calibrated syringe or the sample is weighed.

### Laboratory investigations and serology

Laboratory investigations, also listed in Figure 2, should include:

- full blood count; electrolytes, urea and creatinine; liver function tests; creatine kinase; thyroid function tests
- C-reactive protein, erythrocyte sedimentation rate
- antinuclear, anti-double-stranded DNA, anti-Ro/SSA, anti-La/SSB and anticyclic citrullinated peptide antibodies
- complement C3 and C4 levels
- rheumatoid factor
- immunoglobulin levels, serum

protein electrophoresis

- urinalysis for pH, proteinuria and haematuria, as well as a urine protein-to-creatinine ratio.

Serum cryoglobulins should be measured at diagnosis because cryoglobulinaemia is an important risk factor for increased mortality and lymphoma. Testing should also be performed when cryoglobulinaemia is suspected, such as in patients with cutaneous vasculitis, mononeuropathy or elevated rheumatoid factor, with or without a low C4 level.<sup>3,34</sup>

About 80% of patients with Sjögren disease will have anti-Ro/SSA antibodies, and about 60% will be seropositive for both anti-Ro/SSA and anti-La/SSB antibodies.<sup>30,35</sup> Antinuclear antibodies are present in about 80% of patients and rheumatoid factor in about 60%.<sup>30,31,36</sup> Although rheumatoid factor positivity is not associated with erosive arthritis in Sjögren disease, it is associated with a threefold increased risk of lymphoma.<sup>37</sup>

In patients with risk factors for hepatitis C or HIV infection, testing should be considered because these infections are differential diagnoses for Sjögren disease.

#### 4. 2016 ACR-EULAR CLASSIFICATION CRITERIA FOR PRIMARY SJÖGREN DISEASE<sup>33</sup>

These criteria apply to patients with suspected Sjögren disease who have systemic manifestations typical of Sjögren disease or respond positively to at least one of the following questions.

- Have you had daily, persistent and 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 3 times a day?
- Have you had a daily feeling of dry mouth for more than 3 months?
- Do you frequently drink liquids to aid in swallowing dry food?

The classification of Sjögren disease applies to any individual who has a score  $\geq 4$  when summing the weights from the following items:

- Anti-Ro/SSA autoantibody positivity (3 points)
- Labial salivary gland biopsy with focal lymphocytic sialadenitis and a focus score  $\geq 1$  focus/4 mm<sup>2</sup> (3 points)
- Ocular staining score  $\geq 5$  (or van Bijsterveld score  $\geq 4$ ) on at least 1 eye (1 point)
- Schirmer test  $\leq 5$  mm/5 min on at least 1 eye (1 point)
- Unstimulated whole saliva flow rate  $\leq 0.1$  mL/min (1 point)

Abbreviations: ACR-EULAR = American College of Rheumatology/European Alliance of Associations for Rheumatology; SSA = Sjögren syndrome antigen A.

Serum immunoglobulin G4 levels should also be measured if salivary or lacrimal gland enlargement is present without other typical features or autoantibodies characteristic of Sjögren disease, to rule out immunoglobulin G4-related disease.

#### Salivary gland biopsy and imaging

When Sjögren disease is strongly suspected in a patient who is seronegative for anti-Ro/SSA antibodies, a salivary gland biopsy (usually minor, also known as a labial gland biopsy) is required to confirm the diagnosis. Although minor, this dental procedure should be performed by an operator experienced in excising several minor salivary

#### 5. SJÖGREN DISEASE CLINICAL PEARLS AND PITFALLS

- Sjögren disease may present with systemic features rather than sicca symptoms
- Diagnostic evaluation for Sjögren disease is often incomplete, which can result in delayed or missed diagnoses
- Long-term corticosteroid treatment may be inappropriate and carries significant risks
- Regular dental care and follow up are important
- Systemic manifestations require close monitoring and management

glands; mucosal tissue is not required. The risk of persistent numbness affecting a small area inside the mouth is less than 1%.<sup>38,39</sup>

The pathology request should ask for assessment of focal sialadenitis and reporting of the focus score (the number of foci containing  $\geq 50$  lymphocytes per 4 mm<sup>2</sup>), germinal centre-like structures (which are a risk factor for lymphoma) and other causes of dry mouth, such as sarcoidosis, immunoglobulin G4-related disease or amyloidosis.

If biopsy is unavailable or declined, ultrasound of the major salivary glands can provide additional risk stratification. In Sjögren disease, ultrasound may show multiple hypoechoic areas, hyperechoic linear bands, cysts and calcifications, although the findings are operator dependent.<sup>40</sup>

#### Management

Patients with Sjögren disease are optimally managed by a multidisciplinary team that includes the GP, rheumatologist, ophthalmologist or optometrist, dentist, other subspecialists and allied health professionals if indicated. Patients and their carers should receive relevant information about Sjögren disease and its management, and be connected with patient advocacy organisations, such as Arthritis Australia and Sjögren's Australia, which offer educational resources and support.

Key clinical pearls and common pitfalls in the diagnosis and management of Sjögren disease are summarised in Box 5.

#### 6. CASE STUDY: A WOMAN WITH FATIGUE, ARTHRALGIA AND SICCA SYMPTOMS

A 51-year-old woman presented with a five-year history of chronic fatigue, arthralgia in the wrists and fingers without early-morning stiffness, bilateral dry and gritty eyes, and dry mouth with difficulty swallowing. She also reported dyspareunia and recurrent urinary tract infections but believed these were related to menopause. She had experienced occasional mouth ulcers over the years but no skin rashes, photosensitivity or hair loss. She had a history of miscarriage at nine weeks' gestation and had two healthy teenage children. On examination, she had mild bilateral parotid gland swelling, poor dentition and minimal salivary pooling under the tongue.

Significant subsequent laboratory results included an erythrocyte sedimentation rate of 32 mm/hour, a positive antinuclear antibody titre of 1:320 with a speckled pattern, and positive anti-Ro/SSA and anti-La/SSB antibodies. Rheumatoid factor and cryoglobulins were negative.

She was referred to rheumatology, where the diagnosis of Sjögren disease was confirmed by Schirmer testing and reduced salivary flow; labial gland biopsy was not required. The wrist and finger joints were tender but not swollen, and no synovitis was identified.

She was commenced on preservative-free eye drops four times daily, saliva substitutes and oestrogen pessaries. Short-term simple analgesia, with paracetamol or NSAIDs as needed, was recommended for mild arthralgia, which was considered likely to be secondary to early osteoarthritis. Regular dental, ophthalmology and rheumatology reviews were arranged. She also commenced regular exercise to manage her fatigue.

Abbreviations: SSA = Sjögren syndrome antigen A; SSB = Sjögren syndrome antigen B.

A typical presentation of Sjögren disease, including its diagnostic work-up and initial management, is illustrated in Box 6.

#### Management of sicca symptoms

Initial symptomatic management of dry eyes should include preservative-free lubricant eye drops four or more times daily and warm eye compresses for 10 minutes daily to address concurrent blepharitis. If dry eye symptoms do not

## 7. SJÖGREN DISEASE – QUICK REFERENCE SHEET

### When to consider Sjögren disease

- Unexplained dry eyes, dry mouth or persistent fatigue for more than 3 months
- Multisystem disease without a clear cause, including articular, cutaneous, renal, pulmonary and neurological involvement
- Recurrent parotid gland swelling
- Unexplained dental decay
- Coexisting autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, coeliac disease, autoimmune thyroid disease or primary biliary cholangitis
- The absence of sicca symptoms or antinuclear antibodies does not exclude Sjögren disease

### Key history points

- Ocular symptoms, including gritty, burning, red or painful eyes and blurred night vision
- Oral symptoms, including dry mouth, frequent dental caries and difficulty swallowing dry food
- Parotid gland swelling or pain during meals
- Vaginal dryness, dyspareunia or recurrent urinary tract infections
- Extraglandular symptoms, including fatigue, arthralgia, Raynaud's phenomenon, rashes, neuropathy, cough or dyspnoea
- Pregnancy history, including congenital heart block or neonatal lupus erythematosus

### Examination

- Oral cavity: dry or fissured tongue, reduced salivary pooling, gum recession and dental decay
- Salivary gland enlargement, particularly of the parotid glands
- Skin: dryness or rash
- Chest, neurological and joint examination for systemic involvement or coexisting autoimmune disease

### Initial investigations

- Urine investigations: urinalysis (including urinary acidity, microscopy and assessment for protein and blood) and urine protein-to-creatinine ratio
- Infection screening when indicated: consider hepatitis C and HIV serology if risk factors are present
- Routine blood tests: full blood count; electrolytes, urea and creatinine; liver function tests; creatine kinase; and thyroid function tests
- Inflammatory markers: erythrocyte sedimentation rate and C-reactive protein
- Autoantibodies and complement: antinuclear antibodies, anti-Ro/SSA and anti-La/SSB antibodies, anti-double-stranded DNA antibodies, rheumatoid factor, anticyclic citrullinated peptide antibodies and complement C3 and C4 levels
- Immunoglobulin and protein studies: immunoglobulin levels, serum protein electrophoresis, serum free light chains and cryoglobulins

### Red flags and complications

- Lymphoma: persistent, firm parotid gland enlargement; lymphadenopathy; neuropathy; fatigue; weight loss; or night sweats
- Interstitial lung disease: cough or breathlessness
- Renal disease: renal tubular acidosis with a urinary pH of  $\geq 6$ , low serum bicarbonate or high serum chloride levels, or interstitial nephritis
- Pregnancy complications: congenital heart block associated with maternal anti-Ro/SSA with or without anti-La/SSB

### Management principles

- Arrange early referral of patients to a rheumatologist and ophthalmologist
- Refer pregnant patients who are positive for anti-Ro/SSA, with or without anti-La/SSB, to a maternal-fetal medicine specialist
- Arrange regular dental check ups
- Assess and manage traditional cardiovascular risk factors
- Consider referral to physiotherapy
- Discuss the need for psychologist support
- Provide information about patient support networks:
  - Arthritis Australia: <https://arthritisaustralia.com.au>
  - Sjögren's Australia: [www.sjogrensaustralia.com.au](http://www.sjogrensaustralia.com.au)

Abbreviations: SSA = Sjögren syndrome antigen A; SSB = Sjögren syndrome antigen B.

improve, treatment can be escalated under ophthalmic supervision to ciclosporin eye drops, autologous serum eye drops, punctal occlusion and cauterisation. Dry mouth symptoms are often managed with mechanical saliva stimulants, such as sugar-free lozenges or gum and saliva substitutes, in addition to regular dental review every six months with topical fluoride application.

For ongoing significant sicca symptoms, including an irritating cough caused by upper airway dryness, systemic (oral) pilocarpine can also be used. However, in Australia, this requires repurposing 4% pilocarpine eye drops for oral administration in a small amount of water or using compounded pilocarpine capsules or

lozenges obtained by private prescription, which is costly. The prescribed dose is 5 mg (equivalent to three drops of 4% pilocarpine) four times daily, or a 10mg slow-release lozenge twice daily, with a maximum dose of 30mg daily. It is recommended that treatment start with a low dose, such as one or two drops or one capsule or lozenge twice daily, increasing every few days to two to three drops taken two to four times daily, depending on efficacy and tolerability. Patients should be monitored for side effects such as flushing, sweating or headaches. Avoid the use of pilocarpine in patients with bradycardia or severe asthma, as these conditions may be exacerbated.

Vaginal dryness symptoms in perimenopausal or postmenopausal women can

be managed with topical nonhormonal vaginal moisturisers and oestrogen creams or pessaries.

### Management of systemic manifestations

Systemic manifestations such as inflammatory arthritis and cutaneous lupus are managed with repurposed disease-modifying antirheumatic drugs, such as hydroxychloroquine, methotrexate and leflunomide. Immunosuppressants such as oral corticosteroids, mycophenolate or azathioprine are reserved for severe manifestations, including interstitial lung disease. Organ- or life-threatening conditions are managed with high-dose corticosteroids, rituximab, intravenous

immunoglobulin or cyclophosphamide.<sup>32</sup> Renal tubular acidosis is managed with bicarbonate supplementation.

### Emerging therapies

A large number of novel therapies are currently in development to improve symptoms and slow disease progression, as exemplified by recent phase 3 clinical trials that demonstrated that ichtanalumab, a biologic that inhibits B-cell activating factor receptor from the tumour necrosis factor family and depletes B cells, significantly reduced disease activity with a favourable safety profile.<sup>5,41-43</sup> Telitacicept, a recombinant fusion protein that inhibits both B-cell activating factor and a proliferation-inducing ligand, was recently approved in China for the treatment of Sjögren's disease after positive phase 3 results showed significant and clinically meaningful improvements in systemic disease activity and patient-reported outcomes.<sup>44</sup>

### Lifestyle measures and fatigue

Lifestyle measures in managing Sjögren disease include:

- wearing wrap-around glasses to avoid wind and dust exposure and reduce tear evaporation
- avoiding dry and smoky environments
- avoiding the excessive use of fans or air conditioning
- using a room humidifier
- reducing sugar consumption
- taking frequent sips of water.

Eating soft, moist foods and cutting hard foods into small pieces can be considered to address difficulty chewing because of dental damage and trouble swallowing.

Overwhelming fatigue is common in people with Sjögren disease and can be managed with activity pacing, good sleep hygiene and maintaining physical activity. However, reductions in working hours, social participation, reading and driving are frequent consequences of unrelieved dryness and fatigue in patients living with Sjögren disease, as are large out-of-pocket costs for dental care and off-label medications.<sup>45</sup>

### Management during pregnancy

Pregnancies in mothers who are positive for anti-Ro/SSA antibodies, with or without anti-La/SSB antibodies, should be managed by a maternal-fetal medicine specialist. Hydroxychloroquine use is associated with a 50% reduction in the risk of recurrent neonatal lupus erythematosus and complete heart block. It may be considered for all mothers who are anti-Ro/SSA positive, commencing once pregnancy is confirmed if it is not contraindicated.<sup>29,46</sup> Fetal heart rate should be monitored from 16 weeks' gestation, with weekly monitoring recommended if a previous pregnancy was affected by complete heart block.<sup>29</sup> If complete heart block is detected during pregnancy, urgent specialist care is required and antenatal fluorinated corticosteroids may be considered.<sup>29</sup>

### Cardiovascular risk and associated autoimmune diseases

Traditional cardiovascular disease risk factors should be actively monitored and modified in all patients with autoimmune rheumatic disease, with blood pressure, glycaemia and cholesterol monitored and managed where appropriate. Furthermore, people with Sjögren disease are at a higher risk of coeliac disease, which is up to 10 times more common, as well as autoimmune thyroid disease, such as Hashimoto's thyroiditis and Graves' disease, and primary biliary cholangitis, likely because of shared immunopathology and genetic factors.<sup>47-49</sup>

### Conclusion

Our understanding of Sjögren disease phenotypes, morbidity and mortality, as well as the impact of the disease on quality of life, is rapidly evolving. Addressing the challenges of timely diagnosis of Sjögren disease and management of patients' symptoms at all stages of life is critically important. A quick reference sheet to support GPs in recognising, assessing and managing Sjögren disease is provided in Box 7. New biologic agents targeting the pathogenic immunological pathways involved are currently being investigated in clinical

trials, with the aim of improving the quality of life and reducing disease activity and progression for patients with Sjögren disease.

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A list of references is included in the online version of this article ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)).

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# Beyond sicca symptoms

## Diagnosis and management of Sjögren disease

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