

PRACTICE

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Primary Sjögren syndrome

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Sjögren syndrome is a systemic autoimmune disease causing secretory gland dysfunction. This leads to dryness of the main mucosal surfaces such as the mouth, eyes, nose, pharynx, larynx, and vagina.¹ Sjögren syndrome may be a serious disease, with excess mortality caused by haematological cancer.² The cause of Sjögren syndrome is unknown, but factors postulated to play a role are both genetic and environmental.¹ The disease overwhelmingly affects middle aged women but may also affect children, men, and elderly people. When sicca symptoms appear in a previously healthy person, the syndrome is classified as primary Sjögren syndrome. Sjögren syndrome associated with another underlying systemic autoimmune disorder, such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma is known as secondary or, increasingly, associated Sjögren syndrome.

Sicca symptoms (dry mouth and eyes) are among the most common oral and ocular complaints seen by general practitioners, but even so the disease is often underdiagnosed or misdiagnosed.^{3,4} Although incidence data in primary care are scarce, preliminary reports suggest it may be around two per 1000 patients per year,⁵ with an overall prevalence in Europe of nearly 0.1%.^{6,7} Patients with Sjögren syndrome require a health spend double that of the mean for primary care patients and similar to that for patients with rheumatoid arthritis.^{8,9}

What are the presenting symptoms and signs?

There are three predominant clinical presentations, which may occur at onset or later and often overlap.

Sicca syndrome

Xerostomia (subjective feeling of mouth dryness) and xerophthalmia (subjective feeling of eye dryness) are the key symptoms in the diagnosis of Sjögren syndrome, occurring in more than 95% of patients; a positive answer to at least one of

the three questions about ocular or oral symptoms included in the current classification criteria (box 1) has a positive value of 54–77%, and a negative answer has a negative predictive value of 94–98%.^{10,11} Other oral symptoms include soreness, adherence of food to the mucosa, and dysphagia. Reduced salivary volume interferes with speaking or eating and may facilitate local infection, tooth decay, and periodontal disease. Oral signs include a lobulated or depapillated red tongue and angular cheilitis (fig 1⇓). Xerophthalmia encompasses itching and grittiness, and may be associated with soreness, photosensitivity, ocular fatigue, and reduced visual acuity. Diminished tear secretion may lead to chronic irritation and destruction of conjunctival epithelia (keratoconjunctivitis sicca), with greater susceptibility to ocular infections. Additional sicca symptoms that often coexist with dry eyes and mouth include hoarseness, non-productive cough, skin dryness and, in women, dyspareunia. Nearly 30% of patients may present inflammatory, episodic swelling of the major salivary glands (parotid and submandibular glands).¹²

General symptoms

Abnormal fatigue may be a reason for consultation; it is reported by about 70–80% of patients with Sjögren syndrome and is often related to work disability.^{13,14} Other non-specific symptoms closely associated with fatigue are sleep disturbances, anxiety, and depression, with a prevalence of nearly 15%, 20%, and 40% of patients with primary Sjögren syndrome, respectively.^{14–16} Chronic pain is often associated with polyarthralgia and myalgia, which are reported by more than 50% of patients.¹ Careful assessment is essential, as this set of symptoms is also characteristic of other conditions (including menopause, hypothyroidism, neoplasia, primary depression, and, above all, fibromyalgia). Some patients, especially children and young adults, may present with low grade, self limiting fever.

Methods

We searched Medline for English language articles published between 1 January 1986 and 31 August 2011 for studies in adult humans using the MeSH term "Sjögren's syndrome." Duplicate publications, case reports, experimental studies, and uncontrolled series with fewer than 10 patients were excluded. We also manually searched the reference list of relevant articles retrieved. Study designs were considered in the following order (listed from highest to lowest evidence quality): controlled trials, prospective cohort studies, case-control studies, retrospective studies, and case series.

Box 1 2002 American-European classification criteria for Sjögren syndrome¹¹

1. *Ocular symptoms*—A positive response to at least one of the following questions:
 - a) Have you had daily, persistent, troublesome dry eyes for more than 3 months?
 - b) Do you have a recurrent sensation of sand or gravel in the eyes?
 - c) Do you use tear substitutes more than three times a day?
2. *Oral symptoms*—A positive response to at least one of the following questions:
 - a) Have you had a daily feeling of dry mouth for more than 3 months?
 - b) Have you had recurrently or persistently swollen salivary glands as an adult?
 - c) Do you frequently drink liquids to aid in swallowing dry food?
3. *Ocular signs*—Objective evidence of ocular involvement defined as a positive result for at least one of the following tests:
 - a) Schirmer's test for tear function, performed without anaesthesia (positive result ≤ 5 mm in 5 minutes)
 - b) Rose Bengal score or other ocular dye score (positive result score ≥ 4 on the van Bijsterveld scoring system)
4. *Histopathology*—In minor salivary glands (obtained through normal appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score of 1 (defined as the number of lymphocytic foci (which are adjacent to normal appearing mucous acini and contain >50 lymphocytes) per 4 mm^2 of glandular tissue)
5. *Salivary gland involvement*—Objective evidence of salivary gland involvement defined by a positive result for at least one of the following tests:
 - a) Unstimulated whole salivary flow (<1.5 mL in 15 minutes)
 - b) Parotid sialography showing presence of diffuse sialectasias (punctate, cavitary, or destructive pattern) without evidence of obstruction in the major ducts
 - c) Salivary scintigraphy showing delayed uptake, reduced concentration, or delayed excretion of tracer
6. *Autoantibodies to Ro/SS-A or La/SS-B antigens, or both*

Presence of primary Sjögren syndrome

Patients are classified as having primary Sjögren syndrome when they fulfil ≥ 4 of the 6 criteria; either criterion 4 (salivary gland pathology) or 6 (autoantibodies) is mandatory

Exclusion criteria—Past head and neck radiation treatment, hepatitis C infection, AIDS, pre-existing lymphoma, sarcoidosis, graft versus host disease, use of anticholinergic drugs

Organ specific involvement

Patients may develop several systemic manifestations, either at presentation or later (box 2).

How can the disease be diagnosed?

Early diagnosis may alleviate symptoms and ensure timely treatment of symptoms and complications. Definitive diagnosis of Sjögren syndrome requires the fulfilment of four or more of the current classification criteria (box 1).¹¹ Fulfilment of at least four of these criteria (which must include the histopathological or antibody criteria) has a sensitivity of 93.5% and a specificity of 94%.

Primary care investigation

Clinical—The diagnostic approach for GPs starts by discarding other causes of dry eyes (allergic conjunctivitis, blepharitis, rosacea) and dry mouth, including diabetes, chronic viral infections, dehydration, irradiation of salivary glands, and, especially, drugs (box 3).⁵ The study of impaired saliva and lacrimal secretions is not routinely available in primary care. However, two tests—unstimulated salivary flow measurement, and Schirmer's test—have simple technical requirements readily available in a GP surgery (graduated tube and a small strip of filter paper, respectively), but they require time and practice to be feasible for GPs. For salivary flow measurement, the patient is instructed to spit saliva into a graduated test tube every minute; a quantity of <1.5 mL collected over a 15 minute period indicates impaired saliva secretion. Schirmer's test consists of

a strip of filter paper placed in the lower conjunctival corneal sac; lacrimal wetting of <5 mm of the paper after 5 minutes shows abnormality. Clinical suspicion of Sjögren syndrome should increase when systemic manifestations (box 2) accompany the sicca complaints.

Investigations—Routine blood tests have a role: 25% of patients with Sjögren syndrome have an erythrocyte sedimentation rate >50 mm in the first hour, while 30% have cytopenias (normocytic anaemia, lymphopenia, neutropenia, or thrombocytopenia). These tests are not sufficiently accurate to make the diagnosis, but they may help point to a systemic cause of sicca features.^{17 19} Other tests available in primary care that will suggest an autoimmune origin of the sicca syndrome include hypergammaglobulinaemia, rheumatoid factor, and antinuclear antibodies, which have a low sensitivity (40–69%) but higher specificity and positive predictive values ($>90\%$).^{10 20} These immunological tests may be central in differentiating Sjögren syndrome from non-autoimmune causes of sicca syndrome.

Specialised investigation

To confirm the diagnosis, refer suspected cases of Sjögren syndrome to an ophthalmologist and to a specialist in autoimmune diseases for a specific diagnostic investigation, since the most common symptoms (sicca and general symptoms) are non-specific and extremely common in middle aged women. Ocular and oral involvement should be measured objectively. Complete ophthalmological assessment should include Schirmer's test and corneal staining with colorants (rose Bengal,

Box 2 Major systemic manifestations of Sjögren syndrome (percentages of cases in large case series^{1 2 12 17 18})*Skin*

- Purpura (10–15%) often related to cryoglobulinaemia
- Annular erythema (photosensitive erythematous lesions with indurated borders, see fig 2¹) (5–10%)

Joints

- Non-erosive symmetrical arthritis (15–30%)

Lungs

- Chronic obstructive lung disease (10%)
- Bronchiectasis (8%)
- Interstitial lung disease (5%)

Cardiovascular

- Raynaud's phenomenon (18–37%)
- Pericarditis (<5%)
- Symptoms of autonomic dysfunction

Liver

- Primary biliary cirrhosis (3–8%)
- Autoimmune hepatitis (<5%)
- Fetal congenital heart block in babies of mothers with anti-Ro autoantibodies

Pancreas

- Recurrent pancreatitis (<5%)

Nephro-urological

- Renal tubular acidosis (11%)
- Glomerulonephritis (<5%)
- Interstitial cystitis (<5%)
- Recurrent renal colic due to renal stones (<5%)

Peripheral nerves

- Mixed polyneuropathy (5–10%)
- Pure sensory neuropathy (5%)
- Mononeuritis multiplex (5%)
- Small fibre neuropathy (<5%)*

Central nervous system

- White matter lesions (multiple sclerosis-like disease) (<5%)
- Cranial nerve involvement (V, VIII, and VII) (7%)
- Myelitis (<5%)

Thyroid

- Autoimmune thyroiditis (14–33%)

Haematological

- Autoimmune haemolytic anaemia (<5%)
- Severe thrombocytopenia $<10 \times 10^9/L$ (<5%)
- B cell lymphoma (5–10%)

*Patients with small fibre neuropathy often present with painful burning dysaesthesia of the distal limbs. Because electromyographic studies may be normal, a skin biopsy often confirms the diagnosis.

fluorescein) (fig 3¹) for slit lamp examination to detect conjunctival epithelium destroyed by desiccation. Oral involvement may be evaluated either by the measurement of salivary flow or by parotid scintigraphy. Salivary flow measurement has a sensitivity of 56% and a specificity of 81% for Sjögren syndrome.¹¹ Parotid scintigraphy has greater sensitivity (80%) and specificity (86%)¹⁰ and evaluates the grade of involvement of the major salivary glands; severe involvement (grade IV) at diagnosis is prospectively associated with an increased risk of lymphoma and death.²¹

Immunological study must include determination of autoantibodies to Ro/SS-A and La/SS-B antigens, which are positive in 50–70% of patients and are the only immunological parameter included in the current criteria, with a low sensitivity

(33–46%) but a specificity of 100%.¹⁰ Other parameters that should be tested for, or ruled out, are complement levels, serum monoclonal band, and cryoglobulins (hypocomplementaemia, monoclonal gammopathy, and mixed cryoglobulinaemia are associated with increased risk of lymphoma and death).^{18 19} Finally, minor salivary gland biopsy, although invasive, is highly specific for the diagnosis of Sjögren syndrome, with a sensitivity of 82% and a specificity of 86%,¹¹ and is indicated principally in patients with negative anti-Ro/La antibodies; focal lymphocytic sialadenitis (aggregates of >50 lymphocytes) is the characteristic histopathological feature.¹

Box 3 Drugs causing sicca syndrome

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

When to refer to a specialist

All suspected cases of Sjögren syndrome should be referred to specialist care to confirm the diagnosis. However, specific symptoms suggesting systemic involvement (box 2) may require referral to the appropriate specialist. Be aware of some symptoms or analytical abnormalities that may signal possible systemic complications: these include dyspnoea (interstitial lung disease), paraesthesia or ataxia (peripheral neuropathy), focal neurological symptoms (multiple sclerosis-like lesions, fig 4), recurrent renal colic or raised serum creatinine (interstitial nephritis or glomerulonephritis), and raised alkaline phosphatase or bilirubin (primary biliary cirrhosis). Refer patients with persistent high fever or night sweats, unexplained weight loss, polyadenopathies, or increased or persistent (>1 month) parotid swelling to a haematologist to rule out haematological neoplasia.

What are the complications?

Untreated dry mouth can result in dental loss, oral candidiasis, and periodontal disease, while untreated severe dry eye may result in corneal ulcers and further perforation. Undiagnosed involvement of other organs may delay appropriate therapy, resulting, in some cases, in end stage organ failure (renal failure, pulmonary fibrosis, progressive neurological disease) and death. Objective standardised evaluation of the disease burden has been facilitated by two recently proposed international indexes.^{22 23} Haematological neoplasia is the main complication of Sjögren syndrome, with patients with Sjögren syndrome having a 10–50 times higher risk of lymphoma than healthy individuals, and the largest case series found that 2–9% of patients with primary Sjögren syndrome develop lymphoma.^{18 19 24} Prospective studies have identified parotid enlargement, purpura, cryoglobulins, monoclonal band, and hypocomplementaemia as clinical and immunological risk factors.

How should patients with Sjögren syndrome be treated?

Alcohol and smoking should be avoided, and thorough oral hygiene is essential. Environmental irritants such as smoke, wind, air conditioning, and low humidity may exacerbate ocular symptoms. Treatment of dry eyes should start with preservative-free teardrops and ocular lubricating ointments. The addition of ocular 0.05% ciclosporin in patients with refractory severe disease is supported by controlled trials.²⁵ For dry mouth, mechanical or gustatory stimulation (sugar-free

chewing gum or citric juices) and moisture replacements may be tried first. Controlled trials support the use of oral muscarinic agonists (pilocarpine and cevimeline) for patients with residual salivary gland function.²⁵

Systemic therapy should be tailored to the organ affected and the severity.²⁵ However, the limited evidence available for the drugs most often used with Sjögren syndrome makes firm recommendations difficult. Non-steroidal anti-inflammatory drugs usually provide relief from minor musculoskeletal symptoms; if these symptoms become chronic, add hydroxychloroquine, which has been shown to improve fatigue, arthralgias, and myalgias in uncontrolled observational studies.²⁵ According to evidence from some small retrospective studies and isolated case reports, glucocorticoids or immunosuppressive agents should not be used in these patients, but only in patients with potentially severe systemic involvement.²⁵ Evidence from controlled trials suggests tumour necrosis factor blockers are not efficacious and that B cell targeted agents (rituximab and belimumab) may be more promising therapies.²⁶

How to follow up and monitor

Patients with stable disease limited to mucosal surfaces may require only annual evaluation by their GP or specialist, while those with extraglandular manifestations should be evaluated every six months and those with end organ damage every three months by the specialist in autoimmune diseases.¹ Patients should be routinely asked about cutaneous lesions, night sweats, and weight loss. Routine physical examination should include evaluation of the mouth and eyes to exclude local complications and examination for peripheral lymphadenopathy and enlargement of parotid and submandibular glands, the liver, and the spleen. Yearly laboratory tests should include full blood count, erythrocyte sedimentation rate, and renal and liver function tests as part of the basic investigation for complications. Immunological tests are not necessary in routine follow-up with two exceptions—patients with markers associated with a poor prognosis (low complement levels, mixed cryoglobulinaemia, monoclonal gammopathy), and when there is clinical suspicion of a concomitant systemic autoimmune disease (development of severe Raynaud's disease or cutaneous sclerosis suggesting systemic sclerosis, or erosive arthritis suggesting rheumatoid arthritis).²⁷ Advise fertile women with anti-Ro/La antibodies about the risk of fetal congenital heart block, which has a frequency of <5% and may cause fetal death or the need for a pacemaker in the newborn.

Patient's story

When I was 27, blood tests showed I had an inflamed liver and I was diagnosed with autoimmune hepatitis. Two years later, I started having sicca symptoms, which led to more tests and a final diagnosis of Sjögren syndrome after five more years of visiting a number of specialists. In fact, the first symptoms occurred when I was a teenager, but my doctors didn't know what was wrong. I was very scared and I had many questions and wondered about my future.

It was difficult at first living with this. Sicca symptoms are present every day, with severe periods that may be related to stress or which can be completely unexpected. Various external factors—such as air conditioning; working with computers, smart phones, or tablets; bright or windy weather—repeatedly worsen the symptoms of dry eye, dry mouth, and dry throat, and I often feel quite down. Joint pain and fatigue are terrible and have a big effect on my daily activities, making it difficult to work overtime or even enjoy dinner with my family and friends. Most people don't know about the disease and its consequences, and colleagues, friends, and relatives don't understand why I'm not OK, especially when I seem healthy at first sight.

Now, 12 years later, I take it day by day and derive pleasure from the things I enjoy and can do. I follow a diet and exercise plan, and manage the bad days better than I would have been able to without the knowledge I now have. I think about other people with Sjögren syndrome, because I don't want them to go through the same medical labyrinth of waiting, confusion, and fear—so, in 2006, I cofounded the Catalan Association of Patients with Sjögren Syndrome.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; the work reflects part of research on Sjögren syndrome financed via state funds (Fondo de Investigaciones Sanitarias 08/0103) and a charitable grant (La Marató de TV3 (071810)), but these funders should not have any competing interest in the work.

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Figures



Fig 1 Depigmented red tongue and angular cheilitis



Fig 2 Annular erythema associated with Sjögren syndrome (also called Ro associated cutaneous lesions or subacute lupus-like lesions)

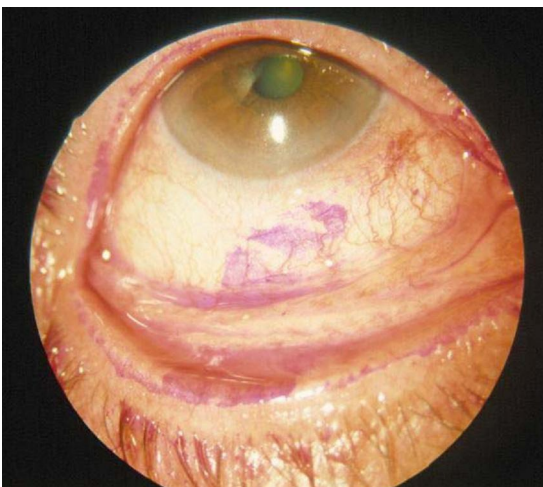


Fig 3 Corneal staining with fluorescein



Fig 4 Magnetic resonance image of demyelinating central nervous system lesions (multiple sclerosis-like)