The General Practice Guide to Autoimmune Diseases

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Sjögren's syndrome

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1 Introduction

Henrik Sjögren described the syndrome in 1933 as a combination of dry eyes and mouth in patients with rheumatoid arthritis. Sjögren's syndrome is a frequent autoimmune disorder (prevalence 0.5–2 %) characterised by lymphocytic infiltration of the salivary and lacrimal glands and leads to dry eyes and mouth, the Sicca syndrome. Secondary Sjögren's syndrome is associated with a connective tissue disease or rheumatoid arthritis, whereas primary Sjögren's syndrome is not associated with other disorders.

The differential diagnosis of Sjögren's syndrome and other causes of the Sicca syndrome is difficult. Sicca syndrome may be a consequence of aging, infections (hepatitis C, HIV), sarcoidosis, or iatrogenic (more than 200 drugs such as tricyclic antidepressants or beta-blockers reduce the saliva and tear flow) and affects up to 10 % of the population [1]. The signs and symptoms of Sjögren's syndrome are summarized in Table 1.

Table 1. Signs and symptoms of Sjögren's syndrome.

Signs of glandular manifestation	Signs of extraglandular disease
Constant thirst	Arthritis
Feeling of dry eyes	Polyneuropathy
Recurrent conjunctivitis	Palpable purpura
Increased rate of upper airway infections	Raynaud's phenomenon
Parotid swelling	

2 Diagnostic criteria

Numerous sets of classification criteria have been proposed, including the San Diego, Copenhagen, Greek or Japanese criteria. In 1993 the preliminary criteria of a European study group formed by members of 26 centres from 12 countries

were proposed [2]. Since then, these criteria have been revised several times. More recently, new American/European consensus criteria were developed from the original criteria and now are widely used [3].

The diagnosis of primary SS requires 4 of the 6 criteria in Table 2, furthermore either criterion 4 or 6 must be included. The diagnosis of SS can be made in patients who have no Sicca symptoms, if 3 out of the 4 objective criteria are fulfilled.

Table 2. The classification criteria of Sjögren's syndrome.

1. Ocular symptoms	– Daily feeling of dry eyes for more than 3 months – Recurrent foreign-body sensation – Tear substitutes are used more than 3 times per day
2. Oral symptoms	– Daily feeling of dry mouth for more than 3 months – Recurrently or persistently swollen salivary glands as an adult – Liquids are frequently used to aid swallowing dry food
3. Ocular signs	– Schirmer's I test performed without anaesthesia ($\leq$ 5 mm in 5 min) – Positive vital dye staining results (van Bijsterveld score of more than 4)
4. Positive lip biopsy findings	– Focal lymphocytic sialadenitis with a focus score more or equal 1 [6]
5. Oral signs	– Abnormal salivary scintigraphy findings – Abnormal parotid sialography findings (diffuse sialectasies without obstruction in the major ducts) – Abnormal sialometry findings (unstimulated salivary flow $\leq$1.5 mL/15 min
6. Autoantibodies	– Positive SSA and/or SSB antibody results

3 Diagnostic measurements for experts

Since complaints about dry eyes and mouth are common, even in the absence of objective problems, the verification of dry eyes and mouth is crucial in the diagnostic work-up of Sjögren's syndrome. Various tests have been proposed:

3.1 Tests to verify dry mouth

Salivary gland scintigraphy

The uptake and secretion of sodium pertechnetate technetium Tc 99m correlates with salivary flow rates and is a good way to measure salivary gland dysfunction. In this test, ^{99m}Tc-pertechnetate is injected intravenously. 15 min after injection, diluted lemon juice is administered orally as a stimulator of the glands. Subsequently, the uptake, activity and washout of the marker in the parotid and submandibular glands is recorded.

Sialography

Diffuse sialectasis may be seen after injection of radiopaque material into the salivary glands. This test is not specific for SS, however sialography using water-soluble media can exhibit sensitivity and specificity ratios similar to that of the biopsy of minor salivary glands. The diagnostic value of parotid sialography for diagnosing SS greatly depends on the skills of the observer. Sialography can exclude obstructions as a differential diagnosis for SS.

Sialometry

In this test, the patients have to swallow all the saliva in their oral cavity and then two cotton balls are placed on the mouth floor, close to the gingival border, where they remain for 15 minutes. Before and after, the weight of the cotton balls is compared. The weight difference is changed from g/min to ml/min, and a saliva production of less than 0.1 ml/min is regarded as reduced. Sialometry is a low cost test, a good measure of the degree of decreased salivary flow and helps to establish xerostomia. It does not distinguish Sjögren's syndrome from other causes of dry mouth.

Saxon's test

This test is a stimulated variant of sialometry. A sterile 10 × 10-cm gauze sponge is folded twice at 90° angles (final size 5 × 5 cm) and placed in a sterile, screw topped 60-ml plastic tube, so that the dry gauze and tube can be weighed. The patient has to swallow to remove any pre-existing oral fluid, then the saliva is collected by asking the patient to chew on the gauze for 2 minutes. Afterwards, the patient replaces the gauze into the same tube, and the amount of saliva produced in 2 minutes can be determined by subtracting the original weight from the weight obtained after chewing.

3.2 Tests to verify the dry eyes

Schirmer's I test

In a Schirmer test, a bent piece of Whatman No. 41 filter paper is placed in the outer one-third of the lower lids of both eyes for exactly 5 minutes. The strip can then be removed, and the length of the strip that was moistened by tears can be measured. A definitive positive (pathologic) result is less than or equal to 5 mm after 5 minutes. This test can be useful to help exclude or confirm significant dryness of the eyes, however it is not specific for Sjögren's syndrome. Furthermore, false-positive results occur.

Rose bengal staining

Rose bengal is an aniline dye that stains devitalized cells. Slit-lamp examination is performed after rose bengal staining to detect abnormal uptake in the cornea. The observer semi-quantitatively ranks the degree of epithelial defects on a scale from 0 to 9 on each eye. A score (the van Bijsterveld score) of at least 4 points is regarded as pathologic.

3.3 Salivary gland biopsy

Minor salivary glands can be removed from an incision of the lower inner lips of the patient and the degree of lymphocytic infiltration can be evaluated histologically. At least 4 salivary gland lobules should be obtained for analysis. The biopsy is the most definitive test for Sjögren's syndrome. Biopsy is not always necessary, but, when the diagnosis is in doubt or if a definitive diagnosis is needed and has a therapeutic consequence, it may be helpful. Biopsy can also help in the differential diagnosis of sarcoidosis. Focal aggregates are the hallmark of Sjögren's syndrome. A focal aggregate consists of at least 50 lymphocytes (predominantly $CD4^+$ cells and, to a lesser extent, plasma cells and macrophages). At least 1 focal aggregate per 4 mm^2 is regarded as pathologic.

4 Requirements for family practitioners

Complaints of dry eyes and dry mouth are extremely common and indeed, more than a third of elderly persons have Sicca symptoms. A common explanation for Sicca symptoms is the use of medications interfering with the gland function, such as antidepressants, anticholinergics, beta-blockers, diuretics, and antihistamines. In the general population these complaints do not correlate with the objective symptoms of dry eyes and mouth. Complaints of Sicca syndrome are associated with depression and fibromyalgia. It is therefore crucial in the diagnostic work-up of patients complaining of dry eyes and mouth, to confirm the complaints by objective tests (such as Schirmer's test or sialometry). When an autoimmune origin

of Sicca syndrome is suspected, the patient should be referred to a rheumatologist for further evaluation. Here, the autoimmune character of Sjögren's syndrome must be verified either by confirmation of the presence of antibodies against SSA and/or SSB in the serum or by salivary gland biopsy.

In the majority of patients, SS is a benign disorder. However, one third of patients have additional extraglandular complications (arthritis/arthralgia, polyneuropathy, vasculitis, purpura, pneumonitis, interstitial lung disease, haematologic involvement).

In addition, patients with Sjögren's syndrome have a higher prevalence of malignant non-Hodgkin lymphoma, in a recent European study as high as 4.3 %. Cryoglobulins and complement consumption are unfavourable prognostic parameters for the development of lymphoma. Patients with these laboratory abnormalities should be followed for development of lymphoma, in particular when anaemia, fever or weight loss occur.

5 Follow up

Most patients can be monitored at follow-up visits every 3 months and, if the patient is stable, up to every 6 months. If acute complications such as vasculitis occur, inpatient care may be appropriate, or follow-up visits must be performed at shorter intervals. During follow-up visits, specific attention must be paid to the efficacy of treatment and to new complications. In general, severe complications such as vasculitis with palpable purpura, leukopenia, renal insufficiency, occur early in the course of the disease, whereas malignancies (non-Hodgkin lymphoma) may develop any time.

Female patients with antibodies against SSA/Ro have an increased risk of complications including neonatal lupus during pregnancy. The risk of congenital heart block is about 2 %, but if one child develops congenital heart block, the risk for congenital heart block during a subsequent pregnancy is approximately 15–20 %.

The prognosis of pSS is generally good, provided there is no malignancy and no severe organ involvement.

6 Management

Treatment is mostly symptomatic [4]. In order to treat dry eyes, artificial tears should be applied. If artificial tears are used at least four times per day, the patients should use a preparation free of preservatives to avoid eye irritation. In very severe cases, temporary plugging of the lacrimal puncta can be performed. Patients should avoid rooms with dry air, not work at a computer for extended periods without a break, and avoid medications with anticholinergic or antihistaminic effects. In order to treat dry mouth, patients should always have liquids available. Sugar-free lemon drops or bubble gums help to stimulate the saliva flow.

Patients should visit a dentist frequently and carefully clean the teeth. In order to treat dry skin problems, skin creams or lotions may be applied. Females may use vaginal lubricants, postmenopausal women vaginal oestrogen creams.

7 Medication

Pilocarpine and cevimeline can stimulate the salivary and lacrimal glands, but many patients complain of side effects such as sweating, diarrhoea and tachycardia.

Whether or not hydroxychloroquine improves the inflammation of glands and the production of saliva and tears has not been clearly established. According to our own experience, it may be beneficial in the early course of the disease when the glands have not yet been completely destroyed. Hydroxychloroquine and NSAIDs are helpful in arthritis as a complication of pSS. Immunosuppressive agents such as cyclophosphamide or azathioprine in combination with corticosteroids are indicated in major organ involvement (vasculitis with neuropathies, glomerulonephritis, interstitial lung disease), but are not useful against dry eyes and mouth. In a recent placebo-controlled study, B cell depletion by rituximab improved both glandular as well as extraglandular manifestations of Sjögren's syndrome [5]. Rituximab may therefore also be considered in severe extraglandular manifestations of Sjögren's syndrome.

8 Diagnostic tests and testing methods

Antinuclear antibodies (ANA), measured by immunofluorescence using HEp2 cells, are present in more than 80 % of pSS patients, but also in up to 20 % of the general population.

ANA are directed against SSA/Ro in approximately 75 % of the patients. These autoantibodies should be identified when Sjögren's syndrome is suspected. Several techniques have been described to detect anti-SSA/Ro (and anti-SSB/La): counterimmunoelectrophoresis (CIE), Western Blot (WB), dot blot (DB) and Elisa. The use of two assays offers the best results in terms of sensitivity and specificity. Antibodies against SSA/Ro are used in the classification of the disorder, but are also present in 50 % of SLE patients and in 1 % of healthy individuals.

Antibodies against SS-B/La are present in 30–50 % of patients with primary SS and in 15–25 % of patients with SLE. Antibodies against SS-B/La rarely occur alone, but usually are observed in patients with antibodies against SSA/Ro.

Rheumatoid factors are frequently found in pSS, but also in 5 % of the population.

9 Further laboratory tests

In patients with vasculitic purpura, cryoglobulins should be measured. Sjögren's syndrome is associated with autoimmune thyroid disease in up to a third of patients. When hypothyroidism is suspected, thyroid-stimulating hormone (TSH) should be measured. In addition, S-electrophoresis helps to detect monoclonal gammopathies and complete blood count should be performed periodically to detect leukopenia.

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