

Sjögren's syndrome

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Introduction

Sjögren's syndrome is a generalised autoimmune disease. It is a disease which is characterised by eye and mouth symptoms caused by an abnormal composition and/or impaired production of tear fluid and saliva. Focal inflammatory infiltrate comprising mainly T-lymphocytes occurs in the lacrimal and salivary glands. In addition to the eye and mouth symptoms, many patients also experience general symptoms. However, these are not characteristic of Sjögren's syndrome because they are not present in all patients and are also frequently found in other diseases. These include: fatigue, arthralgia, Raynaud's phenomenon and hypersensitivity vasculitis.

Abnormalities in the quantity and composition of tear fluid and saliva may also be due to causes other than Sjögren's syndrome. One important cause is medication, particularly diuretics, β -blockers and tricyclic antidepressants. Inflammation of the lacrimal and salivary glands can likewise have other causes.

Prevalence

The prevalence of a disease is largely determined by the criteria used for the diagnosis and the composition of the population group studied. Four recent studies used the European criteria. These showed that approximately 0.6% of the adult population suffers from Sjögren's syndrome.¹⁻⁴ Women are affected by Sjögren's syndrome 9x more frequently than men.

Disease manifestations

The most common symptoms of Sjögren's syndrome are eye irritation, dry mouth, fatigue, joint pain, muscle pain and Raynaud's phenomenon. Other symptoms of the disease occur in lower percentages, see table 1. A number of the symptoms are explained in further detail below.

Eyes

Characteristic eye symptoms are burning and/or itchy eyes and a gritty feeling as though there is sand or a foreign body in the eyes. Patients do not usually complain that their eyes are dry! In addition, the white of the eye may look rather red and the eyelids may sometimes be glued up first thing in the morning. When

exposed to cigarette smoke, Sjögren's patients tend to suffer more intensely - and quicker - from eye irritation than normal people. Eye symptoms increase when reading and when watching television and sometimes also at night. In order to be able to see clearly, it is often first necessary to blink a few times, thereby refreshing the tear film.

Mouth

Although virtually all patients with Sjögren's syndrome suffer from a dry mouth, this complaint is not specific to Sjögren's syndrome.

The most characteristic oral symptom in Sjögren's syndrome is the need to drink when eating (dry) food in order to be able to swallow it. This is known as the *cracker sign*. Patients do not always realise this because they often unconsciously avoid eating certain foods (e.g. a peanut butter sandwich because it sticks to their mouth).

The dry mouth often makes talking difficult and the patient may have a sore throat. There may sometimes be the feeling of having an obstruction in the throat that cannot be swallowed. The poor quality of the saliva may cause a change in the sense of taste and severe dental decay around the gum line.

Infection of the mouth with *Candida albicans*

Table 1. Symptoms occurring in Sjögren's syndrome, grouped according to how commonly they occur

in >50% of patients	in 25-50% of patients
eye irritation	bronchitis sicca
dry mouth	deafness
arthralgia	Raynaud's phenomenon
dry skin	leukopenia
dry vagina	interstitial nephritis
erythematous oral candidiasis	sensory polyneuropathy
flu-like feeling	constipation
painful muscles	irritable bowel syndrome
fatigue	hypersensitivity vasculitis

in 5-25% of patients	in < 5% of patients
antiphospholipid syndrome	chronic atrophic gastritis
arthritis	fibrosing alveolitis
carpal tunnel syndrome	glomerulonephritis
coeliac disease	lymphocytic interstitial pneumonitis
interstitial cystitis	myasthenia gravis
non-Hodgkin's lymphoma	pernicious anaemia
thyroid disorders	pancreatitis
trigeminal neuralgia	uveitis
trombopenia	

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Figure 1. Dry tongue. A burning tongue and cracks in the corners of the mouth indicate a *Candida albicans* yeast infection.

occurs in more than half the Sjögren's patients (figure 1). Symptoms are a burning mouth and tongue, usually with cracks in the corners of the mouth. It is caused by the dryness of the mouth with disruption of the balance between species of candida and the resident bacterial flora in the oral cavity.

Swelling of the salivary glands is seen in approximately 20% of Sjögren's patients, often unilateral and episodic. Figure 2 shows one patient with bilateral swelling and one with unilateral swelling.

The complaint of a dry mouth should not be confused with thirst. Thirst does not form part of Sjögren's syndrome but may be an indication of diabetes mellitus.

Fatigue

For many Sjögren's patients, fatigue is the worst complaint. It often varies with good and bad days and may come on very suddenly. The fatigue may already be present first thing in the morning, usually worsens during the course of the day and improves after a rest. In a small percentage of the patients, fatigue may be the result of *e.g.* anaemia, hypothyroidism, metabolic acidosis due to interstitial nephritis or lack of sleep caused by pain or a dry mouth. However, in the majority of patients it is not possible to establish the precise cause of the fatigue.

Muscle and joint pain

Pain in muscles and joints frequently occurs in Sjögren's syndrome and usually varies in severity and the site of the pain. Inflammation (arthritis) is present if the joints are swollen, hot or red. Arthritis usually occurs symmetrically and mainly concerns the small joints of the hands and feet, seldom large joints such as knees or ankles. The arthritis usually subsides of its own accord within a few weeks and - in contrast to the arthritis occurring in rheumatoid arthritis - causes no damage.

Raynaud's phenomenon

With Raynaud's phenomenon the hands and feet turn bluish-white in the cold. This may even occur sometimes at room temperature or under the shower. The hands may be painful and stiff. This phenomenon may be limited to the fingers (toes), the whole hand (foot) or extend as far as the wrist (ankle).

The blanching is caused by ischaemia resulting from vascular spasms. The blue discoloration is caused by cyanosis. Once the hands and feet warm up, the hyperaemia may turn them red.

Small lesions sometimes occur on the fingertips and take a long time to heal. Raynaud's phenomenon may occur years before the start of Sjögren's syndrome. It is often seen in association with other generalised autoimmune diseases and can also occur independently without any autoimmune disease being present.

Polyneuropathy

Polyneuropathy usually affects the sensory nerves. It causes a numb sensation in particularly both feet, affecting the area covered by socks. There is a clinical relationship with leukocytoclastic vasculitis. The



Figure 2. Swelling of the parotid glands in Sjögren's syndrome. Left: bilateral swelling; centre: detail; right: unilateral swelling in a 9 year old patient with Sjögren syndrome. Note that swelling of the salivary glands is seen in only 20% of Sjögren's patients, often unilateral and episodic.

course of this form of polyneuropathy is usually mild. Motor polyneuropathy has more clinical consequences but is sometimes reversible. This form is rare.

Vasculitis

Histologically speaking, vasculitis in Sjögren's syndrome is usually a leukocytoclastic vasculitis mainly manifested as reddish blue patches (blood leakage) on the lower legs. It is a form of hypersensitivity vasculitis of which the main causes are: infections, drugs, lymphoreticular malignancies, autoimmune diseases and generalised vasculitides. In a large group of patients with hypersensitivity vasculitis, the cause is not found (idiopathic hypersensitivity vasculitis).

Interstitial nephritis

Interstitial nephritis is usually a mild form of inflammation around the distal renal tubules. The result of this inflammation is that too little hydrogen is excreted, causing the urine to become less acid and the body too acid (acidosis). This is known as distal renal tubular acidosis (DRTA). The body compensates for this acidosis by (chronic) hyperventilation. Instead of excreting hydrogen, the kidneys excrete more potassium. This can lead to a potassium deficiency with muscle weakness and symptoms of paralysis.

Hyperventilation causes symptoms such as tingling in the hands, light-headedness, a feeling of pressure on the chest, palpitations or involuntary yawning and sighing.

In a small percentage of patients, interstitial nephritis causes damage to the glomeruli with renal dysfunction. Glomerulonephritis is rare in Sjögren's syndrome. The question then arises as to whether the patient may not (also) have systemic lupus erythematosus.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma occurs in 5-8% of patients with Sjögren's syndrome, usually in salivary gland tissue and/or adjacent lymph nodes. This mainly concerns MALT lymphomas.

Interstitial cystitis

Interstitial cystitis is an inflammatory bladder condition not caused by bacterial infection as in normal cystitis. It may possibly be an autoimmune disease of the bladder.⁵⁻⁷ Like Sjögren's syndrome, it occurs 10x more frequently in women than in men. Characteristic symptoms are pain that increases as the bladder fills and is alleviated when the bladder is emptied, frequent urination (including at night) and urgency. Antibiotics do not help this condition. If the patient has symptoms of cystitis and if interstitial cystitis is suspected, the first thing to be done is a urine culture. If the culture is negative, the patient should be referred to a urologist.

Antiphospholipid syndrome

Antiphospholipid syndrome is caused by antibodies to

Table 2. Generalised autoimmune diseases that may occur in combination with Sjögren's syndrome

disease	characteristic feature
Sjögren's syndrome	specific way it affects the lacrimal and salivary glands
rheumatoid arthritis	specific way it affects the joints
systemic lupus erythematosus	specific way it affects the skin
subacute cutaneous lupus erythematosus	specific way it affects the skin
mixed connective tissue disease (MCTD)	combination of clinical symptoms and anti-RNP
systemic sclerosis (scleroderma)	specific way it affects the skin
CREST syndrome	combination of symptoms

molecules associated with phospholipids and causes thrombosis in veins and arteries. If this occurs in the placenta during pregnancy, it may lead to foetal death. It can also cause thrombopenia and livedo reticularis. Thrombopenia can also occur independently of antiphospholipid syndrome, but is likewise caused by (other) antibodies.

Chronic atrophic gastritis

In chronic atrophic gastritis, the glands in the stomach lining are damaged and reduced in number. This is why it is called atrophic gastritis. If parietal cells are also involved, this leads to achlorhydria and intrinsic factor (IF) deficiency. Since IF is necessary for absorption of vitamin B₁₂ in the small intestine, pernicious anaemia consequently occurs. Pernicious anaemia can also be caused by antibodies to IF, which likewise prevent absorption of vitamin B₁₂.

Other generalised autoimmune diseases

Sjögren's syndrome sometimes occurs in combination with another generalised autoimmune disease. It is then often described as secondary Sjögren's syndrome, but this only means that there are two diseases present and not that the Sjögren's syndrome is the consequence of the other disease. The generalised autoimmune diseases in the table have many symptoms in common. Symptoms that may occur in both Sjögren's syndrome and the other diseases include arthritis, Raynaud's phenomenon, vasculitis and leukopenia. Just as Sjögren's syndrome is characterised by the effect on the (function of) lacrimal and salivary glands, each of the other generalised autoimmune diseases is characterised by its own specific symptoms (table 2).

Patients with a specific generalised autoimmune disease may greatly differ with regard to the occurrence of non-specific symptoms. There are good arguments for the current system of classifying generalised autoimmune diseases, e.g. in relation to expected damage and the best treatment. However, the diseases listed occur so frequently either in combination or in intermediate forms that the question is whether we are really dealing with two separate diseases here.

Etiology and pathogenesis

Sjögren's syndrome is considered to be an autoimmune disease, a disease caused by the immune system. It is unknown why the immune system reacts in this way.

There is so far no evidence that it is a reaction to a viral or bacterial infection, to specific lifestyles, to food or to other environmental factors. The only known factors that increase the risk of developing the disease are: being female, having blood relatives (*e.g.* (mother, aunt or sister) with the disease and having some other related autoimmune disease. In addition certain HLA antigens slightly increase the risk of developing the disease.

The eye and mouth symptoms in Sjögren's syndrome are caused by abnormalities in tear fluid and saliva. Since inflammation in the lip biopsy is usually considered a prerequisite for the diagnosis of Sjögren's syndrome, it goes without saying that this inflammation is found in virtually everyone with the diagnosis of Sjögren's syndrome! Although it seems logical for the inflammation in the glands to be the cause of the symptoms, new insights are giving rise to some doubt. The symptoms of the disease can occur through a number of pathogenetic mechanisms.

Autoantibodies

The function of antibodies is to recognise antigens and provoke local immunological responses. The type of antigen plays an important role in determining the consequences for the individual. If antibodies recognise components of a virus or bacterium, this creates resistance to the infectious disease concerned. If they are directed at harmless external substances (*e.g.* pollen), we describe the response that this provokes as an allergy. If they recognise the body's own cells and cause disease symptoms, we call this an autoimmune disease.

The most well-known autoantibodies in Sjögren's syndrome are antinuclear antibodies, including those to SS-A/Ro and SS-B/La (50-70%) and rheumatoid factors (40%). SS-A/Ro and SS-B/La are proteins found in every cell and play a role in the division of cells. Although it is not certain whether these antibodies can cause disease symptoms in Sjögren's patients, they may possibly increase the skin's sensitivity to sunlight. When women with these antibodies are pregnant, the antibodies also reach the foetus via the placenta. There is then an approximately 10% chance of the baby developing neonatal lupus. The most common symptoms are skin disorders comparable with those of subacute cutaneous lupus erythematosus. The skin problems disappear spontaneously in the first year of life. A serious possible complication is congenital heart block that may even result in intra-uterine foetal death.

Other examples of disease symptoms that can be caused by autoantibodies are leukopenia, thrombopenia and haemolytic anaemia, venous and/or arterial thrombosis (antiphospholipid antibodies) and hyperthyroidism or hypothyroidism (stimulating or blocking antibodies to the TSH receptor).

Immune complexes

Immune complexes are complexes of antibodies, complement proteins and antigens. The formation of immune complexes is a physiological process and a way in which the body rids itself of superfluous substances, *e.g.* bacterial residue. Depending on the composition of the immune complexes (type of anti-

body and antigen, size), they can be formed in the wall of blood vessels and cause vasculitis. This is usually visible in the form of small haemorrhages in the skin on the lower legs.

Focal lymphocytic infiltration

Focal lymphocytic infiltration (localised clusters of lymphocytes) not only occurs in the lacrimal and salivary glands but may also occur in other organs such as the stomach, pancreas and kidneys. In the lip biopsy, focal lymphocytic infiltration is expressed as the focus score for the purpose of diagnosis. A focus is a cluster of ≥ 50 lymphocytes and the focus score is the number of these foci per 4 mm² tissue.

Although the infiltrates may be the cause of functional impairment and damage to the glands, this probably occurs far less frequently than people think. Whereas around half of the surface of a lip tissue specimen normally consists of gland cells, in Sjögren's patients this is around a third. Figure 3 shows the lip tissue specimen with a focus score of 4 of a Sjögren's patient with a very dry mouth. The infiltrates cannot therefore be the only cause of the decrease in saliva formation. Experience with pilocarpine (see further in this article) reinforces the idea that it may well be more complex than hitherto thought.

Lymphomas

5-8% of Sjögren's syndrome patients develop a non-Hodgkin's lymphoma in places where focal lymphocytic infiltrates are present. These are often MALT lymphomas caused by lymphocytes in the mucous membranes. Treatment of lymphomas depends on the type of lymphoma. The prognosis for MALT lymphomas is relatively favourable in comparison with other forms of lymphoma.

Consequences of dry mucous membranes

Dry mucous membranes can themselves be the cause of disorders. The lack of adequate saliva can lead to cervical caries and oral infections with *Candida albicans*. The bacterium *Streptococcus mutans* (that plays a role in tooth decay) is found in greater numbers in the mouths of Sjögren's patients.

Electrolyte imbalance

Interstitial nephritis can be the cause of hyperchloraemic metabolic acidosis with compensatory (chronic) hyperventilation and hypokalaemia with muscular weakness and/or temporary paralysis (see above).

Autoantibodies to muscarinic M3 receptors

On the basis of NOD mice, a strain that develops diseases such as Sjögren's syndrome, American scientists have developed a mouse without B-lymphocytes and therefore unable to make antibodies. Like the normal NOD mice, they developed typical lymphocyte infiltrates in the salivary and lacrimal glands but produced a normal quantity of saliva and tears. This was striking since it was believed that the infiltrates caused the dryness. It was then seen that if antibodies from normal NOD mice or patients with Sjögren's syndrome were injected into the mice without B-lymphocytes, they then developed symptoms of dryness. This there-

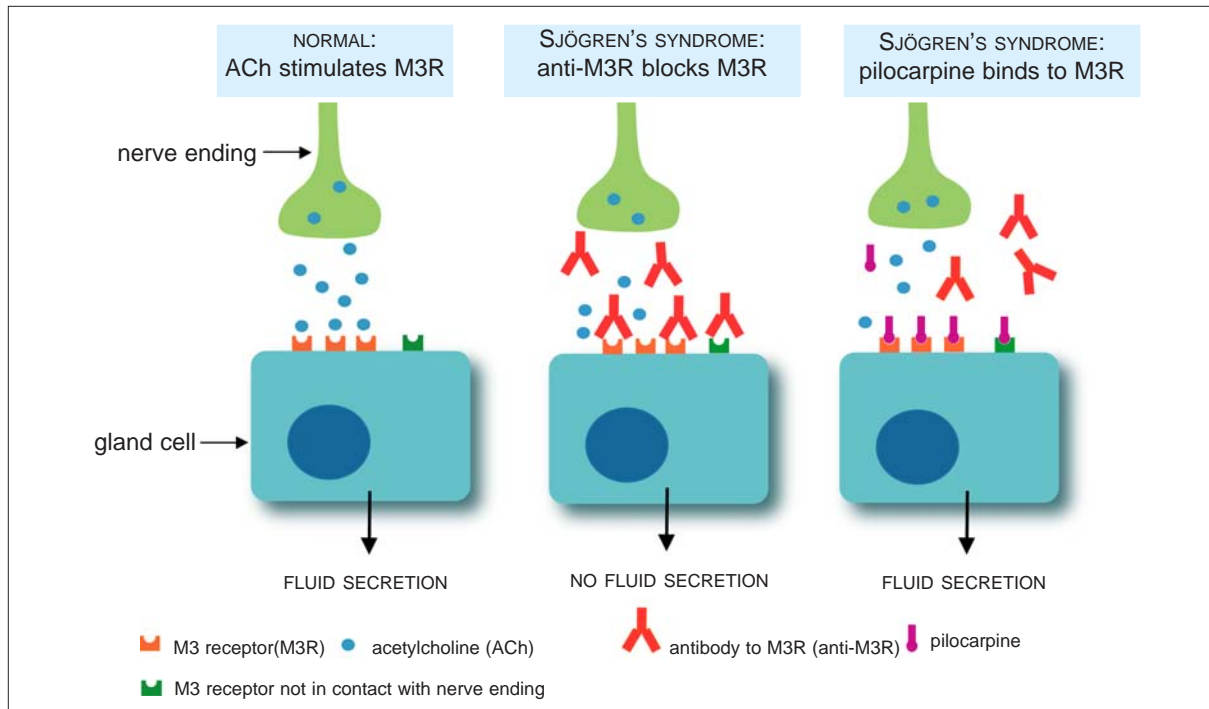


Figure 4. Diagram of the hypothetical cause of dryness symptoms in patients with Sjögren's syndrome. Autoantibodies to the M3 receptor (M3R) block the binding of acetylcholine to the M3R. Pilocarpine binds to the M3R despite the antibodies. Note that pilocarpine also binds to M3 receptors that do not normally bind to acetylcholine. This may explain the effect of pilocarpine irrespective of any role by antibodies.

fore means that it was the antibodies that caused the reduction in fluid secretion and not the inflammation in the glands. It was shown to concern antibodies to the muscarinic M3 receptors that are present, for example, in cells in the lacrimal and salivary glands.⁹ The glands normally secrete fluid when acetylcholine is released from nerve ends and binds to the M3 receptor (see figure 4).

The hypothesis about the role of autoantibodies to muscarinic M3 receptors is interesting because it may explain, for example, why symptoms of dryness can occur in exocrine glands with little or no inflammatory infiltrate and/or damage. It is, moreover, perfectly in

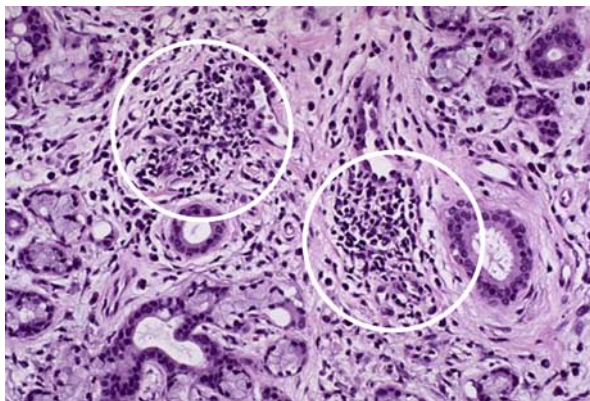


Figure 3. Salivary gland tissue specimen with two focal infiltrates indicated by white circles. Note the small area of the infiltrates in comparison with that of the normal gland tissue.

accordance with the favourable effect of pilocarpine and cevimeline on symptoms of dryness, regardless of the duration of the disease. In recent years, several researchers have tried to develop a usable clinical test to show the presence of antibodies to M3 receptors. This has not been successful so far.

120 kD α -fodrine

Japanese scientists have discovered that a certain strain of mice develops Sjögren's syndrome if the thymus is removed 3 days after birth.⁸ They also found that these mice have antibodies and T-lymphocytes that react with 120 kD α -fodrine, a fragment of 240 kD α -fodrine. 240 kD α -fodrine is a protein that particularly plays a role in fluid secretion by cells, but also occurs in the membrane of most cells in the body. The scientists then injected 120 kD α -fodrine into the mice without a thymus. The result was that these mice did not develop Sjögren's syndrome. 120 kD α -fodrine is also found in the salivary glands of Sjögren's patients, but not in healthy people. In the patients, the antibodies and T-lymphocytes recognised the 120 kD α -fodrine, but not the 240 kD α -fodrine.

α -Fodrine plays a role in apoptosis and the scientists suspect that too much 120 kD α -fodrine may be being formed in cell apoptosis in Sjögren's patients. Many Sjögren's patients appear to have antibodies to 120 kD α -fodrine. More research is necessary to discover the precise significance of this.

Diagnosis

For some years now, the European criteria have been used to diagnose Sjögren's syndrome. These have been

Table 3. Revised international classification criteria for Sjögren's syndrome

I. Ocular symptoms: a positive response to at least one of the following questions:

- Have you had daily, persistent, troublesome dry eyes for >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?

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 3 months?
- Have you had recurrently or persistently swollen salivary glands as an adult?
- Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs - that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

- Schirmer's I test, performed without anaesthesia (≤ 5 mm in 5 min)
- Rose bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system)

IV. Histopathology:

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

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 (≤ 1.5 ml 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

VI. Autoantibodies: presence in serum of the following autoantibodies:

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Rules for classification

For primary SS

In patients without any potentially associated disease, primary SS may be defined as follows:

- a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
- b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
- c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SS

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 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria

Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency disease (AIDS)
Pre-existing lymphoma
Sarcoidosis
Graft versus host disease
Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

revised a number of times and the latest version was published in 2002.¹⁰ They consist of 6 items (table 3), summarised as: ocular symptoms, oral symptoms, eye tests, lip biopsy, imaging or function investigation of the salivary glands and antibodies in the blood.

Sjögren's syndrome can be diagnosed if 4 out of the 6 items are present or 3 of the items 3-6. Items only

Table 4. Differential diagnosis of Sjögren's syndrome (examples)

Causes of dry eyes

- Drugs (β -blockers, diuretics antidepressants)
- vitamin A deficiency
- non-closure of eyelids
- dry environment
- diseases (e.g. sarcoidosis, diabetes mellitus, Parkinson's disease, AIDS)

Causes of dry mouth

- drugs (β -blockers, diuretics, antidepressants, antihistamines, sleeping tablets)
- radiation in the head-neck area
- chemotherapy
- damage to nerves (e.g. facial paresis)
- diseases (e.g. sarcoidosis, diabetes mellitus, Parkinson's disease, AIDS)
- various (including anxiety, dehydration, breathing through the mouth)

Causes of swelling in the large salivary glands

- systemic diseases (sarcoidosis, Wegener's disease)
- infectious diseases (viral: AIDS, mumps, measles; bacterial)
- alcoholism
- anorexia and bulimia
- tumours (malignant: carcinoma, sarcoma, MALT lymphoma; benign: adenoma)
- drugs (isoproterenol)

Diseases with antibodies to SS-A/Ro and/or SS-B/La

- subacute cutaneous lupus erythematosus
- systemic lupus erythematosus (usually patients who also have elements of Sjögren's syndrome)
- neonatal lupus

Diseases that must be excluded according to the European criteria

- past head and neck radiation treatment
- hepatitis C infection
- AIDS
- lymphoma
- sarcoidosis
- graft-versus-host disease
- use of anticholinergic drugs for a preceding period of 4x the half-life of the drug

count if there is no other explanation for them (table 4). A distinction is made between primary and secondary Sjögren's syndrome. The term secondary means that a second generalised autoimmune disease is present. The diagnosis of secondary Sjögren's syndrome can be established if only 3 of the 6 criteria items are present in addition to the other autoimmune disease.

Sequence of investigations

How should the European criteria be applied in practice in order to make a diagnosis. It should first be established whether the eye and mouth symptoms are characteristic of Sjögren's syndrome (see table 3, items 1 and 2). Blood tests should be carried out into other possible causes of the symptoms and for antibodies to SS-A/Ro and SS-B/La for diagnostic purposes (figure 6). Eye tests should also be arranged (Schirmer test and rose bengal dye). Once all the results are known, 2, 3 or 4 criteria items will be present. If there are 4 items, the

Flow chart for the diagnosis of Sjögren's syndrome

An investigational procedure aimed at making a diagnosis is only of value if it can definitively establish or exclude a specific diagnosis, either alone or in combination with other tests. It is possible that at a certain stage of the diagnostic process the decision may be taken to stop any further tests because it is already clear that a specific diagnosis cannot be made, irrespective of the outcome of further investigations. It is also possible that further tests which would be carried out in other situations are no longer necessary because the diagnosis is already sufficiently certain.

When revised classification criteria for Sjögren's syndrome were published in 2002, a chart was drawn up showing the different steps needed to reach a diagnosis. ¹⁰ This is shown in figure 5. Contrary to the Rules for Classification a and b given in Table 3, the absence of

both items 1 (ocular symptoms) and 2 (oral symptoms) leads to the classification of "no Sjögren's". It is also illogical, expensive and patient-unfriendly for a lip biopsy or tests for salivary gland involvement (salivary flow, sialogram or salivary gland scan) to be carried out before antibodies to SS-A/Ro and/or SS-B/La (item 6) have been established, since these can be seen in 50-70% of patients with Sjögren's syndrome. The result of this approach is that in some patients the autoantibodies are unable to make any contribution to the diagnosis because the diagnosis was already established by a lip biopsy or tests for salivary gland involvement.

The author's method is shown in figure 6. Antibodies to SS-A/Ro and SS-B/La will already be determined if item(s) 1 and/or 2 is/are present. A lip biopsy is only carried out if it can lead to a definite diagnosis of Sjögren's syndrome or is

important to help exclude other causes of the symptoms (e.g. sarcoidosis or lymphoma). Since the classification rules require at least item 4 (abnormal lip biopsy) or 6 (antibodies to SS-A/Ro and/or SS-B/La) to be present, it means that item 5: salivary flow, sialogram or salivary gland scan can scarcely be expected to make any significant contribution. Furthermore, a disadvantage of these last tests is that the methods and interpretation are less well standardised.

If fewer than 4 items of the criteria are shown to be present and other causes of the items present can be excluded, a descriptive diagnosis is given that justifies the assumption that the underlying process is the same as that of Sjögren's syndrome (see boxes below in figure 6). Consequently, treatment decisions are made in exactly the same way as in the case of Sjögren's syndrome.

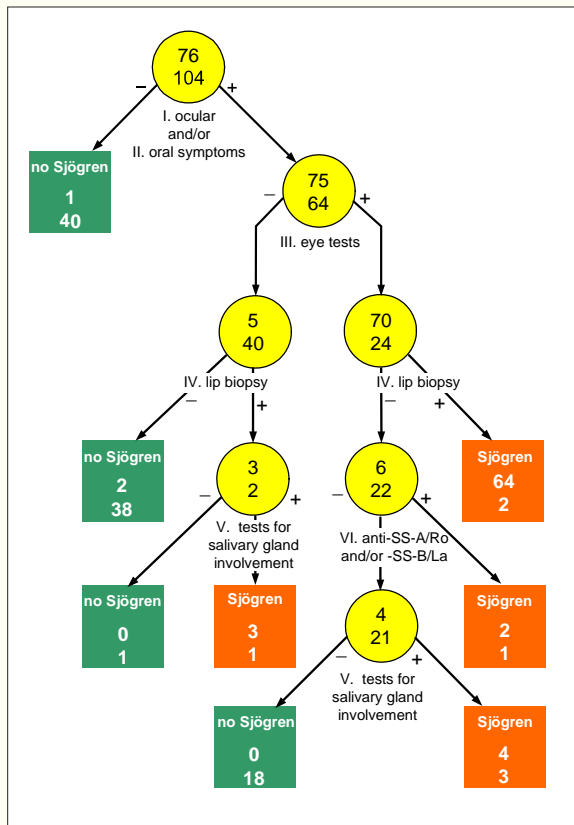


Figure 5. Flow chart for the diagnosis of Sjögren's syndrome (classification tree method) with information about false-negative and false-positive classifications in the final situations according to the European criteria. ¹⁰ The figures in the circles and boxes show the number of patients in the relevant node with Sjögren's syndrome (above) and "no Sjögren's" (below) respectively.

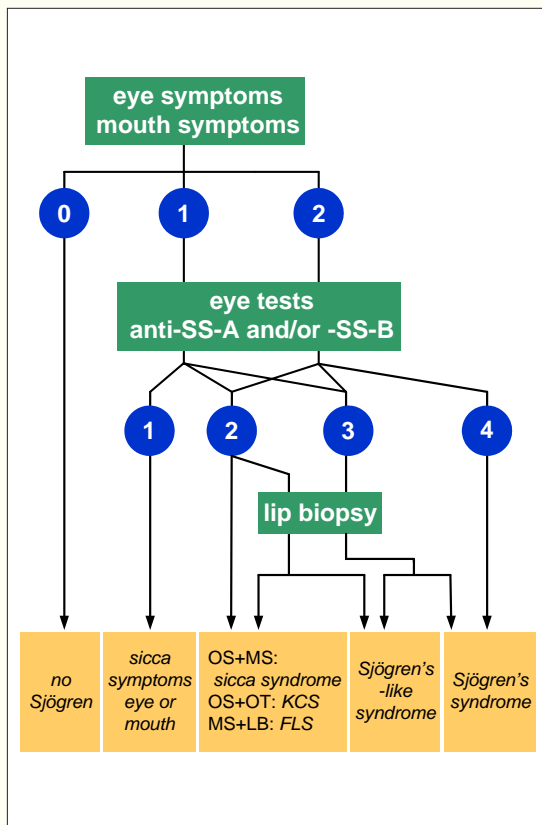


Figure 6. Flow chart for the diagnosis of Sjögren's syndrome as used by the author. See text for further details. The blue circles show the number of criteria items present. Abbreviations: ES: eye symptoms; MS: mouth symptoms; ET: abnormal eye tests; LB: abnormal lip biopsy; KCS: keratoconjunctivitis sicca; FLS focal lymphocytic sialoadenitis;

diagnosis is complete. If 3 are present a lip biopsy needs to be carried out (a focus score ≥ 1 will then give a definite diagnosis). If 2 items are present, no further tests for Sjögren's syndrome need to be carried out because a definite diagnosis is no longer possible. See also box with flow chart for the diagnosis of Sjögren's syndrome.

Patients regularly have fewer than 4 criteria items. If other causes of the signs and symptoms have been excluded (table 4), Sjögren's syndrome may remain as the only probable explanation. Further treatment and monitoring should then be the same as in patients who fulfil all the criteria.

Treatment

Due to the wide variation in signs and symptoms, treatment may greatly differ per patient. Furthermore, considerable individual variations are also seen in the effect of medication on the patient. The possibility and need for treatment depend on the signs, symptoms and risks. The following scenarios are possible:

- a. treatment is necessary for medical reasons
- b. the patient wishes to have treatment for a specific symptom
- c. treatment is neither necessary nor desirable.

The advantage of this classification is that it is clear why treatment is being given, how the result is evaluated and whether the treatment should be continued or stopped after a specific period of time. Indications for treatment can be subdivided into inflammation, dryness and other indications.

Dryness

Sjögren's syndrome is first and foremost an exocrinopathy: an abnormality in the function of exocrine glands. By definition this concerns the eyes and mouth, but the dryness may also occur in other organs such as the nose, bronchial ducts, vagina, skin and intestines.

Some organs can be treated locally, for example the eyes (artificial tears), the mouth (artificial saliva), the nose (ointment) and the skin (cream). Local treatment may be sufficiently effective, particularly if the symptoms are mild. Disadvantages are that they only have a local effect and are not really an adequate replacement for the patient's own tears, saliva, etc.

Systemic treatment plays an important role in the treatment of dryness. Advantages are that it stimulates the formation of the patient's own secretions including the protective substances they contain and that it is often effective in more than one part of the body. Disadvantages are possible side-effects and that these drugs are not effective and/or suitable for everyone. The main drugs used for systemic treatment are pilocarpine and cevimeline (cevimeline is unobtainable in Europe). Positive effects can also be seen from bromhexine 3x 8-16 mg/day or N-acetylcysteine 3x 200 mg/day. If required, pilocarpine can be combined with bromhexine or N-acetylcysteine. We will first take a look at local treatment. Treatment with pilocarpine will be discussed here separately.

Eyes

In many patients, irritation of the eyes can be improved with artificial tears, preferably no more than 4x a day.

If the result is unsatisfactory, it may be worthwhile trying another brand. Some people are unable to tolerate certain preservatives that are added to bottles of artificial tears. It is then worth trying artificial tears containing a different preservative or changing to preservative-free artificial tears. These are supplied in single use containers or in a special bottle (Comod[®] system) which can be used for 3 months once opened.

Mouth

Artificial saliva products are available for local treatment of the mouth. Oral Balance[®] is a gel that is mainly suitable for use at night. A disadvantage is that artificial saliva cannot be used for eating problems caused by dryness. Dryness of the mouth can cause gumline caries. The use of fluoride tablets and/or application of fluoride and frequent dental check-ups, e.g. every 3 months, is important to prevent caries.

Nose

Dry nose symptoms can be treated with physiological salt. In the case of crusts, an ointment containing 10% Emser salt in *oculentum simplex* or Nisita[®] nose ointment can be used.

Lungs

Dryness of the airways can cause *bronchitis sicca*. It is likely that dryness of the airways increases the risk of bacterial infection. Pilocarpine and/or bromhexine can improve this.

Skin

Many patients with Sjögren's syndrome have a dry skin. Showering should be short and the water not too hot. After showering, the symptoms can be considerably improved by applying a cream (20% *vaselinum album* in *cremor lanette I*) onto the wet skin.

Vagina

Dryness of the mucous membranes of the vagina can have different causes, e.g. the menopause, but is also a well-known symptom of Sjögren's syndrome. Treatment with pilocarpine improves the (symptoms of) vaginal dryness in approximately a third of female patients. Lubricants such as Sensilube[®] can be used if required.

Inflammation

Generally speaking, inflammation should be treated if it is likely to cause damage to an organ. If this is only expected in the longer term, the patient can be treated with hydroxychloroquine, usually 400 mg/day for 3 months, followed by 200 mg/day. If there is a risk of irreparable organ damage in the short term, temporary treatment with corticosteroids may be necessary, preferably in combination with hydroxychloroquine. The corticosteroid treatment can be stopped again a few months later. In the case of inflammation that is unlikely to cause permanent damage but nevertheless requires treatment for the symptoms it causes, a prostaglandin synthesis inhibitor can be considered.

Eyes

Inflammation of the lacrimal glands does not usually require separate treatment. If required, the above-men-

tioned treatments can be used. If the surface of the eyes is inflamed, treatment with the usual artificial tears can be supplemented by eye-drops containing an anti-inflammatory agent such as diclofenac, naproxen or cyclosporine.

Mouth

Infection with *Candida albicans* can cause a burning, red tongue and cracks in the corners of the mouth. Tablets often work better than local treatment, e.g. 2-4 weeks 150-200 mg fluconazol or 2x100 mg itraconazole. If the infection keeps returning, preventive treatment can be tried with 150 mg fluconazol 1x a week. Sometimes the candida is resistant to both of these agents. If this is the case, a combination treatment of 2 weeks of 200 mg fluconazol and 250 mg terbinafine daily may solve the candidiasis in many patients. Since candidiasis is partly due to the dryness of the mouth, treatment with pilocarpine can reduce the risk of developing it.

Salivary glands

Approximately 1/3 of patients with Sjögren's syndrome experience unilateral or bilateral swelling of the large salivary glands. The swelling is sometimes very bothersome or painful and consequently requires treatment. It should be borne in mind that infections and malignancies can also cause swelling. The way the swelling develops is an important indication of the most probable cause of the swelling. Swelling caused by Sjögren's syndrome usually develops slowly and comes in waves with 3-12 month intervals or longer. Hydroxychloroquine with pilocarpine and/or bromhexine can be effective. Sometimes a short treatment (e.g. 1-2 weeks) with corticosteroids can be beneficial.

Swelling that occurs suddenly is due to bacterial infection. It is caused by an accumulation of thick saliva in slightly deformed salivary gland ducts. Immediate treatment with antibiotics (e.g. doxycycline, amoxicillin or cotrimoxazole) can limit the damage and lead to a quick improvement. Patients can often prevent infections by massaging the salivary glands for 5 minutes in the morning and taking pilocarpine. Swelling can also be an indication of non-Hodgkin's lymphoma and, if this is suspected, immunohistological investigations are necessary. If swelling continues to form a problem and if there is an increased risk of a non-Hodgkin's lymphoma (high ESR, antibodies to SS-A/Ro and/or SS-B/La, monoclonal or oligoclonal abnormalities), surgical removal of the parotid gland may be the only solution.

Joints and muscles

When considering treatment for arthritis, it should be remembered that Sjögren's syndrome virtually never causes damage to joints. If a second, generalised autoimmune disease is present, it should be investigated whether the arthritis is related to this. Generally speaking, arthritis caused by rheumatoid arthritis will be treated with the aim of preventing damage to the joints. Our own studies have shown that a rheumatoid factor test is of no value for early detection of rheumatoid arthritis in Sjögren's syndrome patients. This test is positive in 40% of patients with Sjögren's syndrome, 98% of whom do not have and will not develop

Treatment with pilocarpine

The purpose of treatment with pilocarpine is to stimulate the salivary glands into making more saliva and the lacrimal glands into making more tear fluid. Other exocrine glands sometimes also function better as a result of this treatment, such as those in the nose, ears. Eustachian tube, oesophagus and other parts of the intestines, skin and vagina. The effect starts half an hour after taking the dose and lasts around 5 hours.

Pilocarpine can be prescribed in the form of capsules made up by the pharmacy or as tablets (Salagen®). The starting dose is usually 4x 5 mg/day. Common side effects of the drug include flushing, sweating and more frequent urination. If these side effects occur, the patients themselves can decide whether they want to continue or stop.

The dose can be increased or reduced, depending on the effect and side effects. In the case of "normal" body weight, the maximum dose is 10 mg 4x per day. This dose can be tried if the effect of the standard dose of 5 mg 4x per day is insufficient and there are no bothersome side effects. Instead of 4x 10 mg, it is also possible to take 8x 5 mg or if necessary 16x 2.5 mg: the advantage of taking a lower dose more frequently is that you avoid peaks of pilocarpine in the blood. This is particularly important if bothersome sweating occurs as a side effect half an hour after taking the pilocarpine.

Pilocarpine can be taken in combination with other drugs. When combined with beta blockers, it is advisable to start with a lower dose because it may cause heart conduction disorders. If the beta blocker is taken for hypertension, it is often useful to replace this by a calcium antagonist or an ACE inhibitor. Since asthma symptoms may sometimes be exacerbated in people with asthmatic bronchitis, this is also a reason to start with a low dose.

Oral symptoms improve in approximately 60% of patients with Sjögren's syndrome and ocular symptoms in almost half the patients.^{12,13}

Pilocarpine comes from a plant, the *Pilocarpus jaborandi*. It acts through binding to the M3 muscarinic receptor on gland cells, as normally occurs with acetylcholine (see figure 5). In patients with Sjögren's syndrome, acetylcholine does not bind successfully to the M3 receptors because there are antibodies to the M3 receptor that block this. The effective action of pilocarpine in 60% of patients with Sjögren's syndrome, irrespective of the duration of the disease, indicates that the diminished function of the exocrine glands is not simply the result of damage to the glands but is principally due to the reduced capacity of acetylcholine to reach the M3 receptor.

rheumatoid arthritis. The test for antibodies to cyclic citrullinated peptide (anti-CCP), on the other hand, is a sensitive and specific indicator of rheumatoid arthritis in patients with Sjögren's syndrome.¹¹

Muscle inflammation (myositis) is rare and mild forms either require no treatment or can be treated with hydroxychloroquine.

Lungs

Lung embolism can be a complication of the antiphospholipid syndrome and is treated with anticoagulants. The lungs may contain lymphocytic infiltrates, comparable with those found in the salivary and lacrimal glands. This condition is known as lymphocytic inter-

Prostaglandin synthesis inhibitors

There are various groups of anti-inflammatory drugs, such as corticosteroids, prostaglandin synthesis inhibitors and others (e.g. hydroxychloroquine and colchicine). There have been new developments, particularly in the field of prostaglandin synthesis inhibitors.

When tissue damage occurs, arachidonic acid is formed from phospholipids of the membrane of leukocytes (white blood cells) with the help of phospholipase A₂. With the help of cyclo-oxygenase-2 (cox-2) this in turn forms e.g. prostaglandins (PGs). These PGs cause inflammatory symptoms such as pain, fever and vasodilatation (figure 7). PG inhibitors reduce the inflammation because they inhibit cox-2. All PG inhibitors on the market until recently also inhibited cyclo-oxygenase-1 (cox-1).

Prior tissue damage is not necessary for the production of cox-1. Cox-1 is normally continuously produced and not only by leukocytes. Cox-1 is needed, for example, for the production of PGs that protect the gastric mucosa and for the function of platelets. PG inhibitors that also inhibit cox-1 consequently sometimes cause damage to the gastric mucosa, while hemostasis is affected in all users. This unfortunate combination of effects is the cause of the gastric bleeding that occurs as a side effect of the PG inhibitors. The risk of this is reduced if a proton pump inhibitor or misoprostol (restores the prostaglandin effect on the gastric mucosa) is taken at the same time.

PG inhibitors are used on a massive scale and many are available over-the-counter. In the United States, it is estimated that they cause 16,500 deaths annually from gastro-intestinal bleeding.¹⁵

In recent years, PG inhibitors have been available that selectively inhibit cox-2, the so-called coxibs. Due to the absence of the cox-1 effect, the risk of gastric mucosa disorders is much smaller and the function of the platelets is not affected. The risk of gastric bleed-

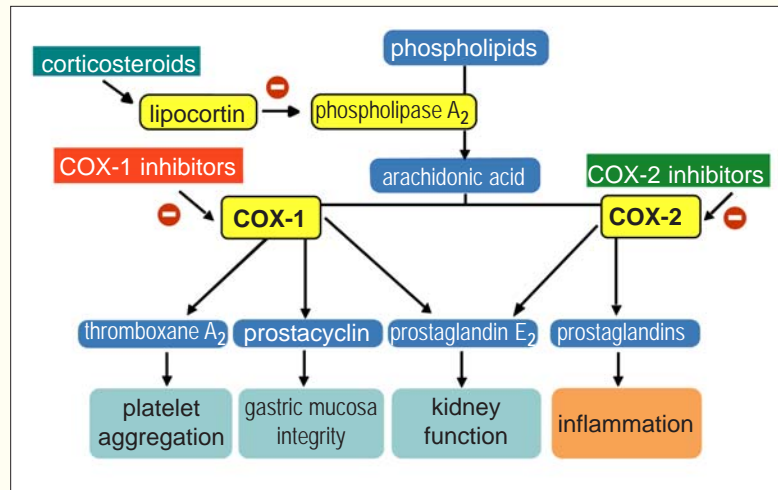


Figure 7. Chart showing the effects of NSAIDs on cyclo-oxygenase-1 and 2 (cox-1 and cox-2 respectively) and corticosteroids on phospholipase A₂.

ing is consequently much less. However, it should be mentioned that the coxibs can sometimes cause stomach symptoms (e.g. dyspepsia) and that in the case of kidney dysfunction and hypertension they inhibit the compensatory mechanisms activated in the kidney by cox-2.

The older PG inhibitors that also inhibit cox-1 are eventually likely to be withdrawn for the treatment of inflammation because there are now equally effective and less dangerous alternatives. The total cost of the use of coxibs is comparable with that of the older drugs if the positive effects on the use of antacids, hospital admissions and surgery are taken into account.¹⁶

In the treatment of cardiovascular disease, inhibition of the function of platelets (a cox-1 effect) is often desirable. This can be achieved in a safe manner by low doses of aspirin. Coxibs naturally do not have this effect and do not offer protection from cardiovascular disease. On the contrary, it has recently been shown that the risk of thromboembolic events may even be increased, possibly depending on the dosage and duration of treatment. Cardiovascular disease or the presence

of cardiovascular risk factors (use of oral contraceptives?) is therefore a contraindication for coxibs. If necessary in these situations a non-selective cox-2 inhibitor can be combined with a proton pump inhibitor and misoprostol.

Well-known side effects of the "old", non-selective PG inhibitors such as urticarial reactions or AERD (Aspirin Exacerbated Respiratory Disease) do not usually occur with coxibs.¹⁷⁻²⁴

The conclusion is that the best choice of NSAID is a coxib. There are however specific contraindications (cardiovascular disease) for the coxibs. The highest doses should be avoided as far as possible.

stitial pneumonitis for which treatment with prednisone is usually necessary, sometimes with the addition of azathioprine. Mild forms may respond well to hydroxychloroquine. It can sometimes lead to a non-Hodgkin's lymphoma in the lungs.

Skin

Skin abnormalities caused by exposure to sunlight can often be treated with hydroxychloroquine 200 mg/dag.

However, hydroxychloroquine can sometimes make the skin more sensitive to sunburn and may also exacerbate any existing psoriasis.

Kidneys

At least three different kidney disorders may occur. Interstitial nephritis does not usually cause kidney dysfunction. Treatment is therefore only necessary for any accompanying acidosis, hypokalaemia (causes muscu-

Treatment with hydroxychloroquine (Plaquenil®)

Hydroxychloroquine (Plaquenil®) and chloroquine (Nivaquine®) are among the safest drugs with anti-inflammatory and disease-modifying properties. In addition to its original use for the treatment and prevention of malaria, hydroxychloroquine has been successfully used for 50 years for the long-term treatment of various chronic conditions such as rheumatoid arthritis and forms of systemic lupus erythematosus. More recently it has been used to treat diseases such as Sjögren's syndrome, sarcoidosis, polymyositis and vasculitides. Although we are talking here about hydroxychloroquine (Hcq), chloroquine has approximately the same effects and side effects: 6.5 mg Hcq is equivalent to 3.0 mg chloroquine.

In Sjögren's syndrome, in addition to its use for inflammatory conditions Hcq can also be used for symptoms without objectively determinable abnormalities.

Inflammatory conditions in Sjögren's syndrome that can be treated with Hcq are those of the salivary glands, muscles, joints, blood vessels and nerves.

Laboratory abnormalities such as increased sedimentation rate, anaemia and increased serum IgG can show an improvement. Hcq also reduces the risk of thrombosis caused by antiphospholipid antibodies, can lower cholesterol levels and probably reduces the risk of a non-Hodgkin lymphoma.

Symptoms for which a trial treatment is worthwhile include severe joint and muscle pain, recurrent flu-like feeling or fever and incapacitating fatigue.

Correct usage of Hcq requires know-

ledge of its properties with regard to its action and side effects. It often takes 2-6 months before an improvement can be seen. The most important, but avoidable, side effect with long-term use is maculopathy. Maculopathy caused by Hcq is a double-sided disorder of the retina with defects in the field of vision. With early diagnosis and stopping the medication, the disorder either recovers or progresses no further.

It is essential to base the dosage on the ideal body weight and kidney function. It is recommended to go no higher than 6.5 mg/kg/day Hcq or 3.0 mg/kg/day chloroquine. Because chloroquines are not well absorbed in fatty tissue, in patients who are overweight the surplus fat should not be counted and calculations should be made on the basis of a body weight that would be normal for the height and gender. Although Hcq can be given even if a patient has eye disorders (with the exception of maculopathy caused by chloroquine), it is nevertheless advisable for an eye check to be carried out in the first year of treatment. This does not need to be done before the treatment starts since retina defects caused by Hcq have never been described in association with treatment for less than 9 months. The timing of the next retina check-up depends on how high the risk of maculopathy is estimated to be. This risk is determined by the dose, the ideal body weight, the kidney function and the length of time for which Hcq has been used.

A patient belongs to the low risk group

if the dose is not higher than the 6.5 mg/kg ideal weight/day Hcq and has been used for less than 5 years. It is important for the upper limit of 6.5 to be lowered in proportion to any kidney dysfunction.

A patient belongs to the high risk group if the dose is above the 6.5 (or lower if the kidney function is diminished) mg/kg ideal weight/day Hcq or if it has been taken for more than 5 years.¹⁴

For the low risk group, an eye check-up is necessary after 5 years of using the drug. For the high risk group an annual check-up is recommended.

A dosage of 400 mg Hcq per day in the first 3 months followed by 200 mg/day appears to work well for many patients. If the symptoms return after reducing the dosage, doses of 200 and 400 mg per day can be taken on alternate days or the patient can return to 400 mg/day.

Other side effects are uncommon and mainly concern allergic reactions (red rash, fever), increased sensitivity to sunburn, pigment changes in the skin and hair loss (recovers after stopping). Psoriasis is usually exacerbated but is by no means an absolute contraindication. During the first days of treatment, patients sometimes have blurred eyesight. This is harmless, has nothing to do with retina disorders and can often be counteracted by halving the dosage in the first week (i.e. usually 200 mg/day). A rare side effect of Hcq is double vision and/or (an increase in) muscular weakness. This may be an indication of subclinical myasthenia gravis.

lar weakness, sometimes paralysis) or hyperventilation. Glomerulonephritis is rare in Sjögren's syndrome, in contrast with systemic lupus erythematosus (SLE). Treatment depends on the type of glomerulonephritis and is similar to treatment in patients with SLE.

Another kidney problem can occur as a manifestation of the antiphospholipid syndrome, in which microthrombi can cause (multiple) ischaemic abnormalities. Treatment consists of anticoagulation aimed at achieving INR levels of 3.0 - 3.5.

Blood vessels

Vasculitis occurs in a quarter of patients with Sjögren's syndrome, usually in the form of hypersensitivity vasculitis (leukocytoclastic vasculitis) with *e.g.* urticaria or purpura especially on the lower legs.

Mild forms of vasculitis do not usually require treatment. If the symptoms are bothersome (*e.g.* pain,

fever) and/or complications occur (*e.g.* ulcers or neuropathy), recommended treatments include: hydroxychloroquine, colchicines, dapsone, cyclosporine, azathioprine or corticosteroids.

Thrombopenia and antiphospholipid syndrome

Thrombopenia occurs in around 10% of patients with Sjögren's syndrome and only requires treatment with corticosteroids and/or intravenous gammaglobulins (IgG) if there is a risk of bleeding. If this proves inadequate, removal of the spleen should be considered. Severe autoimmune thrombopenia is rare and is a reason to suspect systemic lupus erythematosus.

Thrombopenia may also be associated with antiphospholipid antibodies (antiphospholipid syndrome, APS) and is then usually relatively mild. The APS may also be manifested in the form of recurrent thrombosis in arteries and/or veins (lung embolism,

cerebral thrombosis, aseptic bone necrosis) and all kinds of problems in pregnancy. Treatment consists of normal anticoagulation, during pregnancy with lower molecular weight heparin. Thrombopenia in APS may respond well to 38-120 mg calcium carbasalate a day, although this treatment cannot be started in a period in which there is a strong tendency to bleed.

Raynaud's phenomenon

When treating Raynaud's phenomenon, it is essential to keep the whole body warm. Patients should strictly refrain from smoking. Drugs such as ketanserin *e.g.* 1-3x 20 mg/day or nifedipine retard *e.g.* 2x 10 mg/day may sometimes lead to an improvement, with the option of treating only in the winter months. This treatment sometimes has to be stopped due to headache or low blood pressure. If ulcers develop on the hands or feet, 38 mg/day calcium carbasalate may help to accelerate healing and prevent new ulcers. Severe forms of Raynaud's phenomenon can sometimes be successfully treated with bosentan, a drug which inhibits constriction of blood vessels for example.

Prognosis

The course of the disease differs per person. The signs and symptoms often appear to go in waves, without any clearly identifiable reason. From the patient's point of view, the most incapacitating symptom is often the fatigue, followed by irritation of the eyes and a dry mouth.

In general terms, the course of the disease is often stable. After a time, some patients have little bother from the disease and, with a few minor adjustments, can successfully cope with it. Others experience major problems. Most Sjögren's patients lie somewhere in between these extremes.

The disease is not usually life-threatening and life expectancy is normal. However, the fatigue, eye irritation and oral problems have a very negative impact on the quality of life.^{25,26} These consequences of the disease are often underestimated. Serious complications may nevertheless sometimes occur such as a non-Hodgkin's lymphoma, lymphocytic interstitial pneumonitis or glomerulonephritis.

Conclusion

Sjögren's syndrome is a relatively common disease. Diagnosis is often delayed by many years and it may be confused with systemic lupus erythematosus or subacute cutaneous lupus erythematosus. The European criteria are generally used for diagnosis. Although Sjögren's syndrome is characterised by the involvement of lacrimal and salivary glands, virtually all the organs may be involved in this disease. Many aspects of the disease respond well to treatment, *e.g.* with pilocarpine and hydroxychloroquine.

With regard to life expectancy the prognosis is good, but the quality of life is seriously affected in a significant proportion of the patients. The most important complication of the disease is a non-Hodgkin's lymphoma in 5-8% of the patients.

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