

Sjögren's syndrome: an overview

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Sjögren's syndrome is characterized by eye and mouth symptoms caused by an abnormal composition and/or impaired production of tear fluid and saliva.

Inflammation occurs in the lacrimal and salivary glands (figures 1.1 and 1.2) and this means that there is an accumulation of cells (lymphocytes in this instance) in these glands.¹⁻³ In addition to the eye and mouth complaints, almost all patients are also affected by general symptoms. These are not characteristic of Sjögren's syndrome because they are also frequently found in other autoimmune diseases. Examples include pain or inflammation of the joints, fatigue and Raynaud phenomenon.

Sjögren's syndrome is a generalized autoimmune disease. The term *autoimmune disease* means that the disease is caused by the immune system, the body's defence mechanism; *generalized* indicates that more than one organ is involved in the disease.

Abnormalities in the composition and quantity of tear fluid and saliva may also be due to causes other than Sjögren's syndrome. One important cause is medication (see tables 1.1 and 1.2 and chapter 14). Inflammation of the lacrimal and salivary glands can likewise have other causes.

The most common symptoms

The most common symptoms of Sjögren's syndrome are eye irritation, dry mouth, fatigue, joint pain, muscle pain and Raynaud phenomenon.

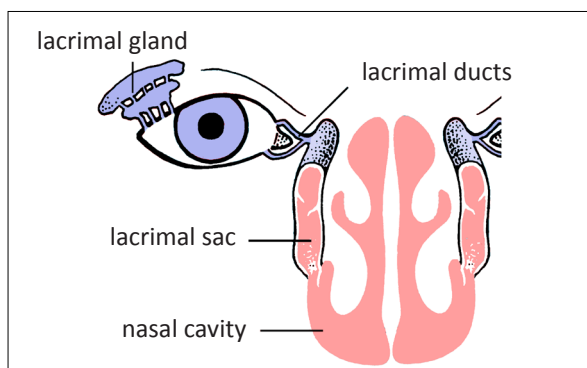


Figure 1.1 The lacrimal gland, lacrimal ducts, lacrimal sac and the duct to the nasal cavity.

Table 1.1 A few causes of dry eyes

- medication
- diseases (including Sjögren's syndrome, sarcoidosis, diabetes mellitus, Parkinson's disease, AIDS)
- vitamin A deficiency
- eyelid abnormalities and/or non-closing eyelids
- dry environment

Eye symptoms

Characteristic eye symptoms are *burning* 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 feel dry! In addition, the white of the eye may look rather red and the eyes may sometimes be glued up first thing in the morning, suggesting *blepharitis* (see elsewhere). Symptoms increase when reading, looking at a screen (e.g. television or computer) or on contact with cigarette smoke.

In order to be able to see clearly, it may be necessary to blink a few times to refresh the tear film. The lacrimal glands may be swollen in some Sjögren's patients.

Mouth symptoms

The most characteristic symptom of the mouth is that patients need to drink when eating dry food in order

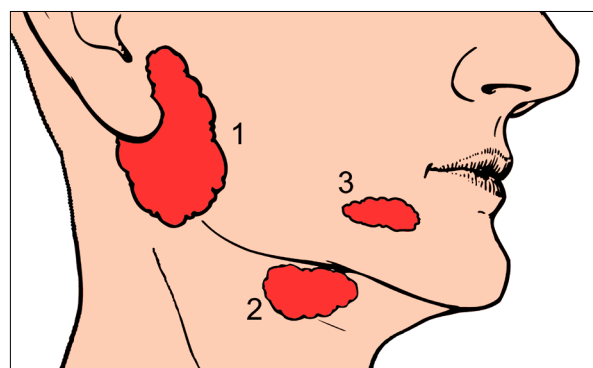


Figure 1.2 The major salivary glands: 1. parotid gland 2. submandibular gland 3. sublingual gland.

Table 1.2 A few causes of a dry mouth

- medication (including antihypertensives, antidepressives, sleeping drugs, diuretics, antihistamines)
- diseases (including diabetes mellitus, Parkinson's, AIDS)
- radiation
- chemotherapy
- nerve damage (facial paresis)
- various (including anxiety, dehydration, breathing through the mouth)



Figure 1.3 Dry tongue. Cracks in the corner of the mouth often indicate a *Candida albicans* yeast infection. A yeast infection may also be the cause of a so-called black hairy tongue (photo right)

to be able to swallow it (this is known as the *cracker sign*). The dry mouth often makes talking difficult and the patient may have a sore throat. There may also be the feeling of having an obstruction in the throat that cannot be swallowed. At night the Sjögren's patient will often have a glass of water next to the bed.

The poor quality of the saliva may be the cause of severe dental decay around the gum line.

A burning mouth and tongue, with cracks in the corners of the mouth (figure 1.3 left) is suggestive of a *Candida albicans* yeast infection. This may be difficult to identify since it is a so-called erythematous candidiasis, mainly with red mucosa and without a white coating.⁴ A yeast infection can also be the cause of a so-called black hairy tongue (see figure 1.3 right).

Swelling of the salivary glands is seen in approximately 20% of Sjögren's patients, often episodic or occurring on one side of the face. Figure 1.4 shows one patient with bilateral swelling and one with swelling on only one side.

Thirst is not the same as a dry mouth. 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 and may be invalidating.⁵⁻¹² It often varies with good and bad days and may sometimes increase very suddenly. Although the fatigue may be present right from the moment of getting up in the morning, it usually increases during the course of the day and improves after a rest. Fatigue is discussed in detail in chapter 6.

Muscle and joint pain

Muscle and joint pain often 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. Joint inflammation usually occurs symmetrically (in other words both left and right) and is more likely to affect the small joints of the hands and feet rather than large joints such as knees or ankles. It usually subsides of its own accord within a few weeks and causes no damage to the joints as in the case of rheumatoid arthritis.

Raynaud phenomenon

With Raynaud phenomenon¹³⁻¹⁶ the hands and feet turn bluish-white in the cold (figure 1.5). This may



Figure 1.4 Swelling of the parotid glands in Sjögren's syndrome. Left: bilateral swelling; middle: the same patient as on the left photo; right: mainly unilateral swelling.

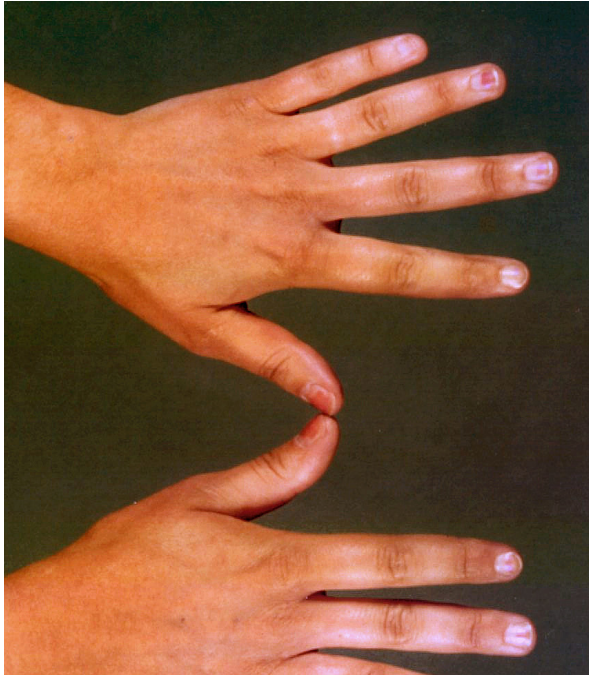


Figure 1.5 Raynaud phenomenon. Note the blanching of the phalanges.

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 impaired blood flow (*ischaemia*) as a result of constriction of the blood vessels. The bluish discoloration occurs when there is an inadequate supply of oxygen to the tissue (*cyano-sis*). Once the hands and feet warm up, they may turn red as the blood vessels dilate (*hyperaemia*). Fissures may occur on the fingertips and take a long time to heal. Raynaud phenomenon may occur years before Sjögren's syndrome or another autoimmune disease manifests itself.

How do you get the disease?

Sjögren's syndrome is considered to be an auto immune disease, a condition caused by the immune system.¹⁷ It is unknown why the immune system does this. There are as yet no indications that it could be a response to a viral or bacterial infection, to specific lifestyles, to food or any other environmental factors. The only known factors that increase the risk of developing the disease are: being female, having blood relatives with the disease (*e.g.* mother, aunt or sister) and having another related autoimmune disease. In addition certain HLA antigens (genes that are best known for the important role they play in tissue transplantation) have a slight influence on this risk (see chapters 3 and 15).

How is Sjögren's syndrome diagnosed?

The diagnosis is made on the basis of criteria. Criteria are agreements relating to the signs and symptoms a patient must have for a diagnosis to be made. These criteria are in the first instance intended to be used for the purpose of scientific research into the disease. In the past many different sets of criteria have been drawn up for Sjögren's syndrome.³ At the present time the so-called American-European criteria are most commonly used (see chapter 4).¹⁸⁻²¹ A major problem is that these criteria only detect a minority of patients with the disease (see also the chapter on incomplete Sjögren's syndrome).

Can the disease be treated?

People often hear that there is no treatment for Sjögren's syndrome. This is not correct. What is true, however, is that the underlying cause of Sjögren's syndrome cannot be removed. But in this respect Sjögren's syndrome does not differ from other diseases such as rheumatoid arthritis or systemic lupus erythematosus.

Despite the fact that there is no treatment that will actually cure the disease for good, treatment can improve the signs and symptoms in many patients. In addition, it is possible to prevent complications from the disease in some of the patients. Treatment is discussed in chapter 5.

What can I expect?

The course of the disease differs per person. The signs and symptoms often appear to go in waves, without any clearly identifiable reason. The most severe symptom is often fatigue, followed by eye irritation and dry mouth. In general terms, changes mainly occur in the first 5 years of the disease, followed by a stable course in the majority of patients (see also chapter 19).

After a time some patients have little bother from the disease and can successfully cope with it, with a few adjustments. Others, however, feel that their life is totally wrecked by their illness. A large number of the patients with Sjögren's syndrome lie somewhere between these two extremes.

Since the disease is not usually life-threatening, life expectancy is more or less normal. However, the fatigue, eye irritation and mouth problems have a very negative impact on the quality of life. These consequences of the disease are often underestimated.

Nevertheless, serious complications may sometimes occur. These include the (malignant) non-Hodgkin's lymphoma (in 5% of patients),^{1,26-32} a specific type of inflammation in the lungs (lymphocytic interstitial pneumonitis) and a specific form of inflammation in

Table 1.3 Prevalence a of Sjögren's syndrome

| <i>source</i> | <i>population studied</i> | <i>diagnostic criteria used</i> | <i>prevalence (%)</i> |
|--|--|--|------------------------------|
| Jacobsson <i>et al</i> 1989 ³³ | population Malmö 52-72 yrs | Copenhagen ⁴¹ | 2.7 |
| Bjerrum 1997 ²⁵ | persons 30-60 yr | Copenhagen ⁴¹ preliminary European ¹⁸ | 0.2-0.8 0.6-2.1 |
| Dafni <i>et al</i> 1997 ²² | women from 18 yr in closed rural community in Greece | validated European ²⁰ | 0.6 |
| Thomas <i>et al</i> 1998 ²³ | general practice population south Manchester - 18-75 yrs - > 54 yr | preliminary European ¹⁸ <i>idem</i> | 3.3 4.6 |
| Tomsic <i>et al</i> 1999 ²⁴ | adults Slovenian population | validated European ²⁰ | 0.6 |
| Bowman <i>et al</i> 2004 ³⁴ | Caucasian women GP lists in Birmingham | | 0.1-0.6 |
| Trontzas <i>et al</i> 2005 ³⁵ | adult white population in Greece <i>idem</i> , female population | American-European ²¹ | 0.15 0.29 |
| Sánchez-Guerrero <i>et al</i> 2005 ³⁶ | ambulatory patients attending a tertiary care centre in Mexico | American-European ²¹ | >13.3 |
| Alamanos 2006 <i>et al</i> ³⁷ | referral adult population north-west Greece | American-European ²¹ | 0.093 |
| Kabasakal 2006 <i>et al</i> ³⁸ | adult women in Turkey | preliminary European ¹⁸ American-European ²¹ | 1.56 0.72 |
| Haugen <i>et al</i> 2008 ³⁹ | population Norway aged 40-44 yr population Norway aged 71-74 yr | preliminary European ¹⁸ validated European ²⁰ preliminary European ¹⁸ validated European ²⁰ | 0.44 0.22 3.39 1.40 |
| Birlik <i>et al</i> 2008 ⁴⁰ | general Turkish population | preliminary European ¹⁸ American-European ²¹ | 0.28 0.16 |

prevalence: % persons in the population with the disease

Why is it called Sjögren's syndrome?

A syndrome is "a set of symptoms which occur together; the sum of signs of any morbid state; a symptom complex. In genetics, a pattern of multiple malformations thought to be pathogenetically related" according to Dorland's, the medical dictionary used by generations of doctors (*Dorland 28th edition © 1994 W.B. Saunders Company*). In practice, however, the term syndrome is only applied to symptoms when the reason why these symptoms occur in combination is unclear.

In 1933, Henrik Sjögren (fig. 1.6) was the first to describe the combination of *keratoconjunctivitis sicca* (KCS, "dry eyes") and dry mouth with inflammation of joints (*rheumatoid arthritis*). It was precisely the occurrence of arthritis in patients with KCS and a dry mouth that was so new (see also chapter 20, answer 16). The term syndrome was therefore the obvious one to apply since the relationship between the eye and mouth symptoms on the one hand and the arthritis on the other was by no means clear.

This relationship is still unclear today but the definition of Sjögren's syndrome has changed. It is now defined as the combination of specific eye and mouth symptoms with objectively determined abnormalities in the (function of the) lacrimal and salivary glands; (rheumatoid) arthritis is no longer an essential element.

However, the combination of signs and symptoms caused by impaired functioning of the lacrimal and salivary glands is much easier to understand, particularly in relation to new insights into the role of muscarinic M3 receptors (see chapter 3). Since arthritis no longer forms part of the definition of Sjögren's syndrome, it is no longer really logical to use the word syndrome. The term Sjögren's disease would in fact be a more appropriate description nowadays.

For historic reasons the name Sjögren's syndrome will continue to be used for the time being despite it has become clear now that cases were described independently by von Mikulicz-Radecki from Poland (fig. 1.7), W.B. Hadden (England), Hutchinson (England) and Fischer (Germany), all in 1888, eleven years before Henrik Sjögren was born. Similar cases were also described by H. Gougerot (1881-1955) in 1925 (dermatologist from France) and A.W. Mulock Houwer (1884-1983) in 1927 (ophthalmologist from the Netherlands).

So, both words in the name Sjögren's syndrome are not correct.



Figure 1.6 Henrik Sjögren (1899-1986), the Swedish ophthalmologist whose name was given to the syndrome.



Figure 1.7 Johannes von Mikulicz-Radecki (1850-1905), the Polish surgeon who described bilateral parotid and lacrimal gland enlargement in 1888.

Prevalence

About 1 out of 250 women between 40-44 years and 1 out of 30 between 71-74 years of age will have Sjögren's syndrome. For men, these numbers are 10 times lower (see text).

the kidneys (glomerulonephritis or inflammation of the kidney filter system).

How common is the disease?

How commonly a disease occurs (*prevalence*) depends on the criteria used for the diagnosis and the composition (male/female; age distribution) of the population being studied. Table 1.3 shows studies that used the Copenhagen⁴¹ or various versions of the European criteria including the most recent American-European criteria.¹⁸⁻²¹ The studies show very different prevalence rates. Recent studies that used the American-European criteria show lower prevalences than earlier studies. As can be expected for a chronic disease with normal life expectancy, the prevalence increases with age.

It is generally agreed that diagnostic criteria do not detect all persons with the disease, due to the high specificity that is required for the use of the criteria for scientific studies (see chapters 4 and 19). Diagnostic criteria for various diseases usually detect about half of

the patients that experts consider to have the disease in question. In my opinion, the most reliable prevalence numbers are those from Haugen *et al* (2008)³⁹ using the validated European criteria (table 1.3). The real prevalence numbers are probably twice as high (see above). This would mean that the prevalence is 0.4 for people between 40-44 yr (4 per 1000) and 2.8 for people between 71-74 yr (28 per 1000). As Sjögren's syndrome affects women about 9x more frequently than men, it can be calculated that about 1 out of 300 women between 40-44 years and 1 out of 40 between 71-74 years of age will have Sjögren's syndrome.

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Salivary glands and saliva

Saliva has many functions in the mouth such as

- protection of the teeth and mucous membranes
- lubrication
- when eating (taste, digestion)
- protection against infection

The mouth has three types of major salivary gland (see figure 1.2):

- the parotid gland
- the submandibular gland
- the sublingual gland

There are also numerous minor salivary glands in the lip, palate and cheeks. Each type of gland produces saliva of a specific composition. The parotid gland makes watery saliva containing various proteins, IgA, lysozyme and amylase. Proteins from the parotid gland, particularly histatines, provide protection against the *Candida albicans* yeast infection for example. The submandibular gland and especially the sublingual gland make mucinous (slimy) saliva. The mucines in this saliva protect the teeth from attack by acids for example. If the function of the parotid gland is impaired, the saliva becomes thicker and more slimy, whereas impaired function of the submandibular and sublingual glands make the saliva more watery.

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Latest additions/changes

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- | | |
|------------|--|
| 06.08.2009 | full conversion to other DTP software |
| 06.08.2009 | change of spelling of Raynaud's phenomenon into Raynaud phenomenon |
| 22.08.2009 | text changes on p. 5 |
| 20.01.2010 | minor text changes |