Sjögren’s syndrome is characterised by abnormalities and impaired functioning of the lacrimal and salivary glands. This causes symptoms of the eyes and mouth. Although in some patients with Sjögren’s syndrome the abnormalities (signs) and symptoms are restricted to the lacrimal and salivary glands, other symptoms also commonly occur.\textsuperscript{1-3} Symptoms not caused by the exocrine glands (glands that secrete fluid) are called extraglandular symptoms.

In this chapter, manifestations are described according to their frequency in Sjögren’s syndrome. Some of the manifestations are also described in more detail in separate chapters, such as fatigue, fibromyalgia and neurological, gastrointestinal, hepatic, pancreatic, pulmonary and bladder disorders.

**Eyes**

Typical symptoms of the eyes are: burning, prickling, a gritty feeling as though there is a foreign body in the eyes and blurred vision. Itching is common but may be due to an allergy, \textit{i.e.} for cosmetic products.

Symptoms often increase when reading and looking at a screen such as television or a computer and are the result of too little and/or abnormal tear fluid composition. Patients rarely complain of dry eyes, and if so, only after an ophthalmologist told them that their eyes were dry!

Inflammation of the salivary glands is known as dacyroadenitis, while the resultant inflammation of the cornea and conjunctiva is called keratoconjunctivitis sicca (KCS), see figure 2.1. Dryness of the eyes is called xerophthalmia.

**Mouth**

Typical problems of the mouth are: dry mouth (lips, tongue, throat), inability to eat dry food without drinking at the same time, difficulty in talking, damage to the teeth (dental decay around the gum line) and yeast infections. These problems are caused by too little saliva and/or abnormal saliva composition.

Inflammation of the salivary glands is called focal lymphocytic sialoadenitis (FLS) while the medical term for dry mouth is xerostomia.

In 20-50% of Sjögren’s patients, one or more salivary glands are enlarged, usually unilateral and episodic.\textsuperscript{4,5} Swelling occurring acutely or within just a few days, particularly if accompanied by redness, pain and fever, is more likely to be a (secondary) bacterial infection of the gland.\textsuperscript{6-9}

**Other features**

Features other than those of the eyes and mouth are seen in differing frequency, some very commonly, others very rarely. A number of these features are discussed below, divided into categories depending on how frequently they occur.

### Table 2.1 Features that frequently (in more than 50%) occur

- arthralgia (painful joints)
- flu-like feeling
- myalgia (painful muscles)
- fatigue
- dry skin
- dry vagina
- *Candida albicans* infection of the mouth
- abnormal/diminished smell and taste
- functional dyspepsia
- irritable bowel syndrome
Features that frequently occur
Table 2.1 shows features that are frequently (in more than 50% of patients) seen. Fatigue, arthralgia (pain in joints) and myalgia (pain in muscles) occur in around 80-90%. These symptoms may be due to an increase of interferon-activity. However, it is extremely important to exclude vitamin D deficiency as a cause of nonspecific musculoskeletal pain. Inflammation of the joints (arthritis), recognisable by the swelling, heat and redness, occurs much less frequently, probably no more than 5%.  

Infection of the mouth with Candida albicans occurs frequently (37-75%) in Sjögren’s syndrome patients. See chapter 1 for the cause and chapter 5 for treatment.

Impaired smell and taste are common in Sjögren’s syndrome patients. Impaired smell occurs in 50% and is probably due to decreased mucin. Taste was significantly reduced in 70% and not affected by age. Taste threshold, unlike smell, is remarkably robust over the lifespan. Within the Sjögren’s group, the finding that the threshold for sweet taste was the least reduced is almost certain because sweet taste is independent of saliva, unlike the other tastes (sour, salty and bitter).

Functional dyspepsia (FD) is defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of organic, systemic, or metabolic disease that is likely to explain the symptoms. The symptom complex of FD includes epigastric pain, early satiety, fullness, epigastric burning, bloating, belching, nausea, and vomiting, but there is considerable heterogeneity in the symptom pattern, both in number and type of symptoms that patients are reporting. The Rome III consensus proposed to consider only early satiation, postprandial fullness, epigastric pain and epigastric burning as typical dyspeptic symptoms.

FD has been diagnosed in 65% of patients with primary Sjögren’s syndrome, as compared to in 39% of healthy controle subjects.

Musculoskeletal pain
All patients with persistent, nonspecific musculoskeletal pain are at high risk for the consequences of unrecognized and untreated severe hypovitaminosis D. This risk extends to those considered at low risk for vitamin D deficiency: nonelderly, nonhousebound, or nonimmigrant persons of either sex.

Plotnikoff, Quigley (2003)
Leukopenia is a reduction in the number of white blood cells. This reduction is usually slight and does not lead to infections or other consequences.

Bronchitis sicca is an inflammatory condition of the lower respiratory organs caused by dryness of the mucous membranes.

Raynaud phenomenon causes attacks of impaired blood circulation in the hands and feet, particularly when exposed to cold temperatures. The hands and feet turn white or blue and sometimes may turn red when they warm up again. A role of interferon in the pathogenesis of Raynaud phenomenon in Sjögren’s syndrome has been suggested.

Vasculitis is an inflammation of small blood vessels. In the case of Sjögren’s syndrome, this mainly concerns blood vessels in the skin. It can cause reddish blue patches (blood leakage), particularly on the lower legs, caused by blood leaking from the blood vessels (figure 2.2).

Interstitial nephritis is generally a mild form of inflammation around the collecting tubules in the kidneys. This results in too little hydrogen being excreted into the urine, making the urine less acid and the body too acid (acidosis). This is known as distal renal tubular acidosis (DRTA) (figure 2.3). This overacidification is automatically compensated for by the lungs via (chronic) hyperventilation whereby the acid is exhaled in the form of carbon dioxide. Symptoms of hyperventilation include tingling in the hands, light-headedness, a feeling of pressure on the chest (tight chest), palpitations or involuntary yawning and sighing. Interstitial nephritis sometimes causes true kidney dysfunction.

Deafness caused by involvement of the auditory nerve was found in a study in 14 of 30 (47%) patients with Sjögren’s syndrome. Nine of the 14 patients had no symptoms, the hearing loss was revealed by tests. Of the five patients with symptoms, one had severe hearing loss and four mild. There was an association between the hearing loss and antiphospholipid antibodies (see below). Other studies confirm that auditory abnormalities are frequent but clinically relevant hearing defects are not common.

Liver diseases have been found in about a quarter of patients with Sjögren’s syndrome. These are chronic infections with HCV (hepatitis C virus) in regions with a high prevalence of HCV infection, such as the Mediterranean area (13%), and autoimmune liver diseases. Primary biliary cirrhosis (PBC) is the most frequent (4%) autoimmune liver disease in Sjögren’s patients. Less frequent are autoimmune hepatitis (2%), sclerosing cholangitis and autoimmune cholangitis. See the chapter on liver and pancreatic disorders.

Impaired gastric emptying and gastroparesis have been diagnosed in 43% and 29% of patients with Sjögren’s syndrome, respectively. For further information, see chapter 9.

Features that sometimes occur

Table 2.3 shows a number of features and disorders that are sometimes seen with Sjögren’s syndrome (in 5-25%).

Arthritis (inflammation of joints) occurs in 15-23% of the patients. The arthritis is symmetrical and usually of the proximal interphalangeal en metacarpophalangeal joints of the hands and corresponding joints.
of the feet. Inflammation of large joints is rare. The arthritis has usually a mild course with remissions and exacerbations. In contrast to the arthritis in rheumatoid arthritis, the arthritis in Sjögren’s syndrome is usually non-destructive.

**Non-Hodgkin’s lymphoma** (NHL) is a collective name for certain malignant diseases of lymphoid tissue (including lymph nodes and lymphocytes). This complication occurs in 5-8% of patients with Sjögren’s syndrome, usually in salivary gland tissue and/or adjacent lymph nodes.1,43-46,86 Baimpa et al conducted a retrospective study of 536 consecutive patients to assess the prevalence of hematologic abnormalities and to identify risk factors for the development of non-Hodgkin lymphoma (NHL).86 Anemia of chronic disease and hypergammaglobulinemia were the most prevalent hematologic manifestations at diagnosis and during the course. Lymphoma was diagnosed in 7.5% of patients. Marginal zone B-cell lymphomas were the predominant histologic type (65%), while diffuse large B-cell lymphomas accounted for 17.5%. The development of NHL could be predicted by the presence of the following clinical and laboratory factors at diagnosis: neutropenia (p=0.041), cryoglobulinemia (p=0.008), splenomegaly (p = 0.006), lymphadenopathy (p=0.021), and low C4 levels (p=0.009). Patients carrying any of these factors had a more than 5-fold increased risk of NHL compared to patients with no risk factors at all.86

**Interstitial lung diseases** occur in about 25% of the patients with primary Sjögren’s syndrome. Early clinical manifestations include dyspnea and dry cough. Lung diseases in Sjögren’s syndrome are discussed in the chapter on pulmonary disorders.

**Interstitial cystitis** or bladder pain syndrome is an inflammatory bladder condition that is not caused by bacterial infection as in “normal cystitis”. It may possibly be an autoimmune disease of the bladder (see chapter on urogenital disorders).47-49

The **antiphospholipid syndrome** has only recently been recognised as a separate entity.50-52 It is caused by antibodies against phospholipid-associated molecules and may cause thrombosis in both veins and arteries. If this occurs in the placenta during pregnancy, it may lead to foetal death. It can also cause thrombopenia (too few blood platelets) and a skin disorder known as livedo reticularis or mottling (figure 2.4).

**Thrombopenia** can also occur separately from the antiphospholipid syndrome, but is likewise caused by (other) antibodies.

**Thyroid disorders** are more common in Sjögren’s syndrome than in the general population.5,53-55,62,84 In a recent study, 479 Hungarian patients with primary Sjögren’s syndrome were investigated for the presence of thyroid disorders.62 **Hashimoto’s thyroiditis**, an inflammatory condition of the thyroid gland, was diagnosed in 30 patients (6.26%), 16 of whom had overt hypothyroidism (decreased thyroid hormone secretion) and 13 subclinical hypothyroidism (thyroid hormone secretion still normal due to increased TSH secretion). Data on Graves’ disease are given in the next column.

**Carpal tunnel syndrome** is caused by entrapment of the nerve that regulates movement and feeling in the thumb, index finger and middle finger. This nerve (median nerve) passes through a narrow duct in the wrist which is where entrapment can occur (see chapter on disorders of the nervous system).

**Chronic atrophic gastritis**56-59 is an inflammation of
the gastric mucosa (stomach lining) with an increase in the number of lymphocytes and plasma cells in the tissue. As a result, the glands in the stomach lining are damaged and reduced in number (atrophy). The involvement of parietal cells (figure 2.6) leads to a reduction in the formation of hydrochloric acid (*achlorhydria*) and intrinsic factor (IF). Since IF is necessary for absorption of vitamin B12 further along in the small intestine, this leads to pernicious anaemia. 

**Pernicious anaemia** can also be caused by antibodies against IF, likewise preventing absorption of vitamin B12. However, pernicious anaemia occurs in fewer than 5% of patients with Sjögren’s syndrome.

**Coeliac disease** (gluten sensitive enteropathy) is characterized by small-intestinal mucosal injury and nutrient malabsorption in genetically susceptible individuals in response to the dietary ingestion of wheat gluten and similar proteins in barley and rye. Coeliac disease affects about 1% of the population but only 10-15% of these individuals have been diagnosed and treated. See chapter on gastrointestinal disorders.

**Features that rarely occur**

Table 2.4 shows features and disorders that rarely (in fewer than 5%) occur in Sjögren’s patients.

**Graves’ disease**, a thyroid disease caused by autoantibodies to the TSH-receptor (figure 2.5) with hyperthyroidism or subclinical hyperthyroidism

<table>
<thead>
<tr>
<th>Features that rarely (in fewer than 5%) occur</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- autoimmune hepatitis (2%)</td>
<td></td>
</tr>
<tr>
<td>- glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>- Graves’ disease (4%)*</td>
<td></td>
</tr>
<tr>
<td>- interstitial nephritis with impaired kidney function</td>
<td></td>
</tr>
<tr>
<td>- lymphocytic interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td>- myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>- osteomalacia</td>
<td></td>
</tr>
<tr>
<td>- pancreatitis (inflammation of the pancreas)</td>
<td></td>
</tr>
<tr>
<td>- pernicious anaemia</td>
<td></td>
</tr>
<tr>
<td>- primary biliary cirrhosis (4%)</td>
<td></td>
</tr>
<tr>
<td>- prostatitis</td>
<td></td>
</tr>
<tr>
<td>- pulmonary arterial hypertension</td>
<td></td>
</tr>
<tr>
<td>- sclerosing cholangitis</td>
<td></td>
</tr>
<tr>
<td>- small fibre neuropathy (3%)</td>
<td></td>
</tr>
<tr>
<td>- uveitis</td>
<td></td>
</tr>
</tbody>
</table>

*not statistically different from the prevalence in the general population.
How to deal with features that may possibly form part of Sjögren’s syndrome

Sjögren’s syndrome does not offer protection against other diseases and disorders. A Sjögren’s patient consequently has the same risk of developing other diseases and disorders as anyone else. Do not therefore be tempted to attribute everything to Sjögren’s syndrome.

The disadvantage of doing this is that the true cause may never be found and usually no solution either. When faced with features that cannot automatically be attributed to Sjögren’s syndrome, the best approach is first to have it investigated.

Only when a diagnosis has been made should you examine the possibility of a relationship with Sjögren’s syndrome. This can best be explained on the basis of an example. Imagine that someone with Sjögren’s syndrome has had stomach pain for 6 weeks and is anaemic. A few possible causes could be a gastric or duodenal ulcer, stomach cancer, inflammation of the gastric mucosa (lining of the stomach) due to the use of certain anti-inflammatory drugs, or chronic atrophic gastritis. The correct diagnosis can only be reached after inspection of the stomach using a flexible camera (gastroscopy). This investigation has to be carried out by an experienced doctor who can interpret the results.

A gastroscopy allows the oesophagus, stomach and duodenum to be inspected while small pieces of tissue can be removed (biopsy) for microscopic examination from areas here abnormalities are seen. Once a diagnosis has been made, it can then be interpreted in relation to the Sjögren’s syndrome. Generally speaking, this can only be done properly by a doctor with experience of Sjögren’s syndrome. In the case of stomach cancer, there is no direct relationship with Sjögren’s syndrome. Erosion (superficial damage to the gastric mucosa) or gastric ulcers may be the result of certain anti-inflammatory drugs (see also chapter 5). Where chronic atrophic gastritis is concerned, a relationship with Sjögren’s syndrome can be considered likely.

In other words, correct interpretation can only take place if a diagnosis has first been made without the features immediately being associated with Sjögren’s syndrome.

Don’t let Sjögren’s syndrome be blamed for everything! Be on your guard when someone without real knowledge of Sjögren’s syndrome blames an unidentified complaint on Sjögren’s syndrome.

Figure 2.7 Structure of the eye (see text).
This disease is generally caused by antibodies against the acetylcholine receptor. The symptoms are mainly muscle weakness and fatigue (see chapter 7).

**Interstitial nephritis** is usually a mild disorder of the renal (kidney) tubules. In rare instances, the kidney function may be decreased.

**Glomerulonephritis** (inflammation of the kidney filter) can decrease the kidney function, but is rare in patients with Sjögren's syndrome. In these cases, the question to be considered is whether the patient might not in fact (also) have systemic lupus erythematosus.

**Uveitis** is inflammation of the uvea of the eye. The uvea consists of the iris, ciliary body and choroid, see figure 2.7. The different parts of the uvea may be inflamed separately or together. Anterior uveitis (iritocyclitis) is inflammation of the front parts of the uvea, iris and ciliary body. Posterior uveitis (choroiditis) is inflammation of the back part of the uvea: the choroid. **Panuveitis** is inflammation of both the front and back parts of the uvea. The symptoms of uveitis may consist of light intolerance, blurred vision, pain and redness of the eye. Uveitis may present itself suddenly with redness and pain in the eye, but can also occur slowly with increasingly blurred vision but only a little pain or redness.

**Osteomalacia** (softening of the bones) is a bone disorder, comparable with rickets in children. Symptoms are pain in the bones and fractures. There are various possible causes such as calcium, phosphate or vitamin D deficiency, acidosis and certain drugs. It is a rare disorder in Sjögren's syndrome, but is associated with distal renal tubular acidosis (see above).

**Small fibre neuropathy** occurs in about 3% of patients with Sjögren's syndrome. It is a peripheral neuropathy characterized by the impairment of thinly myelinated A and unmyelinated C-fibres. Both somatic and autonomic fibres may be involved, thus leading to sensory and autonomic neuropathies. Isolated autonomic neuropathies are rare. Symptoms of somatic nerve fibre dysfunction, such as burning, pain, and hyperaesthesia, frequently prevail over those related to autonomic nerve fibre impairment. This may explain why the term “painful neuropathy” is often used as a synonym (this is not correct as painful symptoms can also be a feature of large fibre neuropathies).

**Features of which the relationship with Sjögren’s syndrome is uncertain**

Table 2.5 shows common disorders where the relationship with Sjögren’s syndrome is uncertain.

**Depression** is by no means rare but the relationship with Sjögren’s syndrome is uncertain.

**Sarcoidosis** (Besnier-Boeck disease) is discussed in chapter 20, questions 37 and 43, and organizing pneumonia in the chapter on pulmonary disorders.

**Dizziness** can have many causes, such as hyperventilation, that may be indirectly related to Sjögren’s syndrome.

**Impaired concentration** commonly occurs but it is uncertain whether this is due to Sjögren’s syndrome. It may be caused by fatigue. Since acetylcholine and muscarinic receptors (see chapter 3) play a role in storing information in the memory, this could be a possible explanation.

**The relationship between Sjögren’s syndrome and other generalized autoimmune diseases.**

Sjögren’s syndrome sometimes occurs in combination with other generalized autoimmune disease (see table 2.6). It is then often referred to as secondary Sjögren’s syndrome. This only means that there are two diseases present and not that the Sjögren’s syndrome is the characteristic feature

<table>
<thead>
<tr>
<th>disease</th>
<th>characteristic feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>rheumatoid arthritis</td>
<td>way it affects the joints</td>
</tr>
<tr>
<td>systemic lupus erythematosus (SLE)</td>
<td>way it affects the skin</td>
</tr>
<tr>
<td>subacute cutaneous lupus erythematosus (SCLE)</td>
<td>way it affects the skin</td>
</tr>
<tr>
<td>mixed connective tissue disease (MCTD)</td>
<td>specific combination of features and antibodies to RNP</td>
</tr>
<tr>
<td>systemic sclerosis (scleroderma)</td>
<td>way it affects the skin</td>
</tr>
<tr>
<td>CREST syndrome (limited systemic sclerosis)</td>
<td>specific combination of features</td>
</tr>
</tbody>
</table>
consequence of the other disease.

The generalized autoimmune diseases mentioned have many features in common. Features that may occur in both Sjögren’s syndrome and the diseases listed in table 2.6 include inflammation of the joints (arthritis), Raynaud phenomenon, vasculitis and lowered white blood cell count (leukopenia). Just as Sjögren’s syndrome is characterised by the effect on the function of the lacrimal and salivary glands, each of the other generalized autoimmune diseases is characterised by its own specific features.

Patients with a specific generalized autoimmune disease may greatly differ in the non-specific features they may have. There are good arguments for the current system of classifying generalized autoimmune diseases, for example in connection with expected damage and the best treatment. However, the diseases mentioned occur so frequently either in combination or in intermediate forms that the question arises as to whether we are really dealing with two separate diseases here. It is possible that there may be one disease with features that fall within the definition of two diagnoses.

The way in which generalized autoimmune diseases are classified is principally a question of mutual agreement and consensus. The current classification and definitions will undoubtedly change in the future on the basis of results of scientific research.

References

2002; 29:726.