Introduction

Sjögren syndrome (SS; Gougerot–Sjögren syndrome) is an autoimmune disorder in which immunocytes damage the salivary and lacrimal glands, and other exocrine glands. Dry mouth and dry eyes are seen with lymphoid infiltrates in these and other exocrine glands, and serum autoantibodies (Fig. 37.1).

SS has two main forms (Table 37.1):

- Primary Sjögren syndrome (SS-1), in which dry eyes and dry mouth are seen, in the absence of a connective tissue disease. This is uncommon and sometimes termed ‘sicca syndrome’, but the latter term is also used non-specifically for dry mouth and eyes.
- Secondary Sjögren syndrome (SS-2), which comprises dry eyes and dry mouth together with a connective tissue disease, is more common. The connective tissue association is usually with (in descending order of frequency):
  - rheumatoid arthritis (RA)
  - systemic lupus erythematosus
  - polymyositis
  - scleroderma.

Incidence

SS itself is uncommon, although the very rarity may lead to underdiagnosis.

Age

SS can affect any age, but the onset is most common in middle-age or older.
Common and important oral conditions

Sex
The majority of patients affected by SS are women.

Geographic
There is no known geographic incidence to SS.

Predisposing factors
See Figure 37.2.

- Sjögren syndrome may have a genetic basis: there is association especially to HLA class II antigens HLA-DRB1*15-DRB1*0301 and TAP1-0101 TAP2-0101. SS is sometimes found in other family members and it is also found more commonly in families that have members with other autoimmune disorders.
- A Sjögren-like syndrome can be produced by viruses [Epstein-Barr virus, hepatitis C virus, HIV, human T lymphotropic virus 1 (HTLV-1)].
- A Sjögren-like syndrome can be produced by graft-versus-host-disease (see Ch. 40).

Aetiology and pathogenesis

- The antigen in SS is unknown, but viruses may be implicated.
- The autoimmune response usually mainly affects exocrine glands, particularly the salivary, lacrimal, and vaginal.
- The lungs, brain, nerves, joints, kidneys, thyroid and liver can also be affected in SS.
- Autoantibodies found in SS are commonly against:
  - IgM (rheumatoid factor – an IgG antibody against IgM)
  - ribonucleoproteins, especially Sjögren syndrome-A (SS-A or Ro), and SS-B (La)
  - others antigens such as:
    - alpha-fodrin
    - alpha-amylase
    - muscarinic M3 receptor
    - carbonic anhydrase
    - actin
    - salivary duct. However, in sicca syndrome (where oral symptoms are typically more severe) these are less frequently found than in secondary SS, suggesting they may be causally unrelated to the duct damage.

Fragmentation of autoantigens such as La (SS-B) or alpha-fodrin during apoptosis (cell death) causes the redistribution of these autoantigens, leading to the production of the autoantibodies in SS (Fig. 37.3).

- SS appears to be the result of lymphocyte-mediated destruction of exocrine glandular acini, which starts with periductal infiltration initially mainly by B but later mainly by T lymphocytes (Fig. 37.4). The distribution of the membrane pore channel (water channel) protein aquaporin-5 is abnormal in SS, perhaps as a result of paracrine effect of TNF-alpha, and the neurogenic regulation of the salivary gland also becomes impaired (Fig. 37.5). One theory is that Sjögren syndrome is caused by a deficiency of suppressor T lymphocytes and subsequent overactivity of B lymphocytes, with release of interleukin-10 (IL-10) and the production of autoantibodies. Anti-muscarinic 3 receptor antibody plays an important role in cholinergic hyper-responsiveness in SS. CD40/CD40L (CD40 ligand) and Bcl-2 family proteins, in tandem with B cell-activating factor (BAFF), protect infiltrating lymphocytes from apoptosis.

- Although the gland acini atrophy, the duct epithelium tends to persist and proliferates – sometimes to the extent that the duct lumens may become obliterated, producing islets of epithelium known as ‘epimyoepithelial islands’. The fully developed lesion of SS in major glands thus appears as a dense mass of lymphocytes interspersed by islands of epithelium, a pattern termed the ‘benign lymphoepithelial lesion’ (BLL). Occasionally, BLL exist in the absence of serological and other features of SS.
- B-cell overproduction may eventually lead to lymphoma (Fig. 37.6).

Clinical features

Sjögren syndrome has a clinical spectrum that extends from an organ-specific autoimmune process to a systemic disorder. The early manifestations may be non-specific, such as fatigue, arthralgia, and Raynaud’s phenomenon, and it can be 8–10 years from the initial symptoms to full-blown SS. Since the signs and symptoms can be so subtle
Sjögren syndrome

and non-specific, a thorough history and careful physical examination are mandatory.

SS presents mainly with (Box 37.1):

- eye complaints, including sensations of grittiness, soreness, itching, dryness, blurred vision or light intolerance. The eyes may be red with infection of the conjunctivae and soft crusts at the angles (keratoconjunctivitis sicca). The lacrimal glands may swell
- oral complaints (often the presenting feature), including:
  - xerostomia: often the most frequent and obvious clinical component, although not all patients complain of dry mouth (Fig. 37.7)
  - soreness or burning sensation
  - difficulty eating dry foods, such as biscuits (the cracker sign)
  - difficulties in controlling dentures
  - difficulties in speech: there may be a clicking quality of the speech as the tongue tends to stick to the palate
  - difficulties in swallowing
  - complications such as unpleasant taste or loss of sense of taste; oral malodour; caries; candidiasis; sialadenitis.

Oral and salivary gland examinations are important. The mouth may appear dry, and on examination there may be:

- tendency of the mucosa to stick to a dental mirror
- food residues (Fig. 37.8)
- lack of salivary pooling
- frothiness of saliva and absence of frank salivation from major gland duct orifices
- a characteristic tongue appearance; lobulated, usually red, surface with partial or complete depapillation
- in advanced cases – obviously dry and glazed oral mucosae.

Oral complications

- Unpleasant taste, loss of sense of taste or malodour.
- Candidiasis is common and may cause soreness and redness of the oral mucosa or angular cheilitis.
- Dental caries tends to be severe, affect smooth surfaces and is difficult to control.
- Ascending (suppurative) sialadenitis is a hazard.
- Salivary gland enlargement is not uncommon in Sjögren syndrome. It is:
  - usually caused by the SS inflammatory process
  - intermittently caused by bacterial ascending infection (acute sialadenitis; Fig. 37.9)
Common and important oral conditions

- Occasionally massive and associated with enlargement of the regional lymph nodes, a condition called 'pseudolymphoma'.
- Rarely due to lymphoma.

Mikulicz's disease (MD) is the term given to persistent salivary and lacrimal gland enlargement associated with raised serum immunoglobulin G4 (IgG4) and prominent infiltration of IgG4-expressing plasmacytes in the lacrimal and salivary glands. It is characterized by few autoimmune reactions and good responsiveness to corticosteroids; complications include autoimmune pancreatitis, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis and Riedel's thyroiditis.

**Box 37.1**

**Sjögren syndrome main features**

**Oral signs and symptoms**
- Dry mouth
- Cracker sign
- Burning
- Salivary swelling and sialadenitis
- Caries
- Candidiasis
- Abnormal taste
- Malodour

**Ocular signs and symptoms**
- Foreign body sensation
- Inability to tear
- Light intolerance

**Others**
- Fatigue
- Fever
- Kidney, muscle, nerve, liver, joint, thyroid involvement
- Connective tissue disease
Extraoral complications

- Connective tissue disease in SS usually precedes the onset of dry eyes and dry mouth, and, therefore, patients presenting with dry eyes and dry mouth alone probably have primary SS, unless a connective tissue disease manifests within about 1 year. The connective tissue disease in secondary SS is typically longstanding and should be clinically obvious; rheumatoid arthritis is the most common.

- Extraglandular complaints of SS can include (Fig. 37.10):
  - Raynaud phenomenon
  - arthralgia
  - myalgia
  - fatigue
  - skin ulceration or rash
  - dyspnoea
  - dry vagina
  - bruising, bleeding and purpura
  - numbness and other neurological features.

- Associations of SS can include:
  - autoimmune (Hashimoto’s) thyroiditis
  - gastro-oesophageal reflux disease (GORD)
  - primary biliary cirrhosis
  - malignant or pseudomalignant lymphoproliferation. Mostly in primary SS, these are B-cell lymphomas, which result from B-cell lymphoproliferation in mucosal-associated lymphoid tissue (MALT lymphoma) and which may develop into monoclonal gammopathies (such as Waldenstrom’s macroglobulinaemia). Pseudolymphoma or frank lymphoma should be suspected when there is persistent salivary gland enlargement, lymphadenopathy or lung nodules. Mixed monoclonal cryoglobulins may be found, and when these contain rheumatoid factor cross-reactive for V kappa IIIb related or VHI-related idiotypes, they may be markers for lymphoma.
Common and important oral conditions

A subjective feeling of dry mouth (xerostomia) is common, although reduced salivary flow (hyposalivation) is not always confirmed by objective studies (see Ch. 8). Indeed, of older people 16–25% complain of xerostomia – usually caused by drugs. If SS is suspected; however, specialist referral is warranted since investigations may be needed, and the differential diagnosis may include:

- viral infections:
  - hepatitis C virus
  - HIV
  - HTLV-1
  - EBV
- sarcoidosis
- glandular deposits in:
  - haemochromatosis
  - lipoproteinaemias
  - amyloidosis
- lymphomas.

The diagnosis of SS is mainly on the history, clinical examination and investigation, including:

- ocular symptoms
- oral symptoms

In pregnancy in SS, the autoantibodies may move transplacentally and cause fetus/infant heart block.

Fig. 37.10 Sjögren syndrome – extraglandular complications

Diagnosis

Eye examination

Examination of the eyes by a specialist is most important (Table 37.2).

Autoantibodies and other blood tests

Autoantibody assays can be extremely helpful in diagnosis, and are readily available, inexpensive and fairly non-invasive. SS-A (Ro) and SS-B (La) antibodies are found especially in primary SS, may have diagnostic value in patients with unexplained parotid swelling and may antedate clinical evidence of Sjögren syndrome by months or years.

Blood tests may be indicated to:

- examine for SS-A and SS-B
- assess erythrocyte sedimentation rate (ESR) or plasma viscosity
- exclude anaemia
- examine IgA immune complexes
- exclude similar syndromes seen in infection with hepatitis C virus, EBV, HTLV-1 or HIV.

Salivary gland examination

Salivary gland examination, functional studies and biopsy may be indicated (Box 37.2, Table 37.2, Algorithms 37.1 and 37.2).

Salivary flow measurements (sialometry)

These are relatively simple and non-invasive, but are non-specific, and not especially sensitive. Objective evidence of diminished salivary flow in Sjögren syndrome includes a:

- decreased resting secretion rate of whole saliva <1.5ml in 15 minutes: this is more closely associated with symptoms of xerostomia than are stimulated flow rates. The test should be standardized by being carried out: after overnight fasting; first thing in morning; no food or drink for at least 1 hour before the test; no smoking for at least 1 hour before

The American–European diagnostic criteria (revised) for Sjögren syndrome are shown in Box 37.2.

- ocular signs
- autoantibodies
- salivary gland involvement
- histopathology.
the test; and with the patient being asked to dribble all their saliva into a measuring container for 15 minutes.

- decreased stimulated flow rates: usually regarding flows of <0.5 ml per gland in 5 minutes to 5 ml per gland in 10 minutes as abnormal. Use various means of stimulation, such as 10% citric acid dropped onto the tongue, and collect parotid saliva using a Carlsson-Crittenden cup placed over Stensen’s papilla.

### Box 37.2

**Sjögren syndrome American–European diagnostic criteria**

SS is diagnosed if 4 of these 6 criteria are positive (especially if histopathology and serology are positive) or if there are ocular symptoms or oral symptoms, plus any 2 of the other 4 criteria:

**Ocular symptoms**
At least one of these:
- daily persistent troublesome dry eyes for >3 months
- recurrent sensation of sand or gravel
- need to use teardrops >3 times daily

**Oral symptoms**
At least one of these:
- daily feeling of dry mouth >3 months
- recurrent or persistently swollen salivary glands as adult
- frequently drink liquids to aid swallowing dry foods

**Ocular signs**
At least one of these:
- Schirmer <5mm in 5 minutes
- Rose–Bengal score >4

**Histopathology**
Focus score >1 on LSG

**Salivary gland involvement**
At least one of these abnormal:
- scintigraphy – reduced concentration/uptake/excretion
- sialography – diffuse sialectasis
- unstimulated whole salivary flow <1.5 ml in 15 min

**Serum autoantibodies**
At least one of these:
- SS A (Ro)
- SS B (La)

See Vitali et al (2002) for detail
*Focus = cluster of 50 or more lymphocytes in a labial salivary gland (LSG)
†Focus score = average number of foci in a 4 mm² area

### Table 37.2

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Typical findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sialometry</td>
<td>Reduced</td>
<td>Non-specific, but readily available</td>
</tr>
<tr>
<td>Salivary gland biopsy</td>
<td>Focal lymphocytic infiltrate</td>
<td>More specific</td>
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<tr>
<td></td>
<td>Acinar atrophy</td>
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<tr>
<td></td>
<td>Fibrosis</td>
<td></td>
</tr>
<tr>
<td>Sialography</td>
<td>Sialectasis</td>
<td>Non-specific, but often available</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>Reduced radionuclide uptake</td>
<td>Non-specific, but expensive</td>
</tr>
</tbody>
</table>

### Salivary gland biopsy

Biopsy of salivary glands can be useful in the diagnosis of Sjögren syndrome. Biopsy of major glands involves a skin incision and slight possibilities of facial nerve injury, scarring and salivary fistula. Therefore, minor salivary glands are usually biopsied.

Minor glands in the palate and lower lip are accessible, but the latter site is preferred both from the aspects of patient comfort and access for the operator, and also because the extent and pattern of histopathological changes on labial salivary gland (LSG) biopsy correlate with those in parotid and submandibular glands.

The LSG biopsy technique involves: local analgesia; simple linear incision in the lower labial mucosa just to one side of the midline; at least five lobules of LSG are blunt dissected out and removed; and one or two sutures may be placed to ensure haemostasis. There are few adverse effects except occasional minor hypoesthesia.

Focal sialadenitis is the characteristic histopathological feature. LSG histology, if used with a focus score (FS), provides a reproducible and objective evaluation of severity of inflammation. Other features such as fibrosis or fatty atrophy, duct dilatation and hyperplasia, however, are non-specific. A focus is defined as an aggregate containing 50 or more mononuclear cells: the FS is the number of such aggregates in each 4 mm² area. The mononuclear cells are predominantly T-helper inducer cells. The FS is reliable only where gland lobes with acinar atrophy and interstitial fibrosis are excluded, and where an adequately large specimen is examined. The threshold FS generally used for diagnosis of SS is one focus per 4 mm², though others use slightly higher thresholds. Focal sialadenitis in an adequate LSG biopsy (at least 4–5 lobules) appears to be the most disease-specific and sensitive diagnostic method.
Common and important oral conditions

Sialography
Sialography has the following characteristics:
- shows sialectasis (this is the most typical finding, it is most sensitive using oil-based contrast media and is seen particularly in parotid glands and may correlate with histological scores and scintigraphy)
- specificity is low
- time-consuming
- may be painful
- may produce hazards, such as granulomatous reactions or infection.

Salivary scintiscanning
Salivary scanning (scintigraphy) has the following characteristics:
- Shows diminished radionuclide uptake and spontaneous secretion, or secretion following citric acid or pilocarpine stimulation
- Is relatively non-invasive
- Examines both parotid and submandibular glands simultaneously
- Changes correlate with sialographic, flow rate and LSG histological changes, but are non-specific
- Quantitative registration of uptake and secretion phases with correction for vascular background might improve the diagnostic and monitoring value of salivary scintigraphy.

Ultrasonography
This is proving to be a useful method for evaluating salivary gland involvement in Sjögren syndrome and may replace other diagnostic techniques, such as sialography or salivary scintigraphy.

Magnetic resonance imaging
This can be helpful in showing soft tissue changes.

Sialochemistry
- Analysis of saliva composition (sialochemistry) for the diagnosis and monitoring of salivary disease has had some enthusiastic proponents, but has been of no

Algorithm 37.1  Dry mouth diagnosis
Sjögren syndrome

Management

- Sjögren syndrome remains an incurable condition, since no therapeutic modality has been identified that reliably modifies the course of the disease. Recently there have been attempts to control the underlying autoimmune pathogenic mechanisms of lymphoid infiltration and cytokine release.
- Patient information is an important aspect in management.
- Any connective tissue or other disorders should be treated by a physician.
- Patients with severe extraglandular manifestations are usually treated by a physician with systemic corticosteroids and other immunosuppressive drugs.
- The patient should be followed up regularly, particularly because of the possible complication of lymphoma, which may manifest with:
  - firm tender persistent salivary swelling
  - lymphadenopathy
  - nodular lung lesions
  - cough
  - dyspnoea
  - hepatosplenomegaly.
- Other aspects of care include the following:
  - The use of a humidifier in the bedroom.

practical value. It could prove to be of value in monitoring the disease process in view of the non-invasive nature. The diagnostically and prognostically most promising recent sialochemical findings have been of raised levels of:

- lactoferrin
- beta₂-microglobulin
- interleukin-6
- lysozyme
- sodium, chloride, albumin, lactoferrin, IgA and IgG (however, these are non-specific and rarely correlate with salivary flow or histological changes).
**Salivary substitutes** may help symptomatically.
- Use chewing to stimulate salivation.
- It is wise for the patient to avoid:
  - mouth-breathing;
  - any drugs that may produce xerostomia (e.g. tricyclic antidepressants; alcohol (including in mouthwashes); smoking; caffeine (coffee, some soft drinks); dry foods, such as biscuits (or moisten in liquid first); spicy foods; and oral healthcare products containing sodium lauryl sulphate, which may irritate the mucosa.
- Salivation may be stimulated by using:
  - chewing gums (containing xylitol or sorbitol, not sucrose);
  - diabetics sweets; cholinergic drugs, such as pilocarpine or cevimeline that stimulate salivation (sialagogues) – which should be used by the specialist as discussed in Chapter 7; and transglossal electrical stimulation.
- Salivary substitutes may help symptomatically. Various apart from water are available, including: methylcellulose; Saliva Orthana and Oralbalance carpine or cevimeline that stimulate salivation (sialagogues) – which should be used by the specialist as discussed in Chapter 7; and transglossal electrical stimulation.
- For dry eyes, methylcellulose eye drops or, rarely, fluconazole are particularly useful since they contain fluoride (see Ch. 5) and mucin. However, there may be religious or cultural objections to use of mucin by some Muslims, Hindus, Jews and Rastafarians:

**Websites**

Arthritis Link: [http://www.arthritislink.com/arthrlinks.htm](http://www.arthritislink.com/arthrlinks.htm)
Sjögren’s Syndrome Foundation: [http://www.sjogrens.org](http://www.sjogrens.org)
British Sjögren’s Syndrome Association: [http://www.bssa.uk.net](http://www.bssa.uk.net)

**Further reading**


