Sjögren's syndrome

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Abstract

Sjögren's syndrome is a systemic autoimmune disorder characterized by focal inflammation of the exocrine glands, leading to dry eyes and dry mouth. Two forms of the syndrome have been defined: primary (pSS), in which dysfunction of the exocrine glands occurs in the absence of other autoimmune diseases, and secondary (sSS), in which patients suffer additional autoimmune processes, especially connective tissue disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and scleroderma. About 70% of patients with pSS have anti-Ro and/or anti-La autoantibodies. Hypergammaglobulinaemia is also common and a proportion of patients have systemic involvement. Better use of symptomatic therapies can make a big difference to patients and there is also current interest in whether anti-B cell therapy could be effective in treating pSS.

Keywords Alternative criteria; assessment; biologic therapy; diagnosis; histology; pSS; Sjögren's; therapy

What's new?

- The Sjögren's syndrome registries — to promote basic science and clinical research in pSS
- Clinical assessment tools — the ESSDAI and ESSPRI have been developed
- The use of ultrasound in pSS
- The American–European Consensus Group classification criteria continue to be the key diagnostic tool for Sjögren's syndrome but the SICCA–ACR criteria provide an alternative
- Clinical trials of anti-B cell therapy are being pursued by a number of research groups as a potential therapy for pSS
- Inhibitors of BAFF, including anti-BAFF monoclonal antibodies (TACI-Ig or BAFF-R-Ig) are currently being evaluated

Sjögren's syndrome (SS) is a systemic autoimmune disorder characterized by focal lymphocytic infiltration of the exocrine glands, leading to dry eyes and dry mouth.[1] It occurs either as a primary disorder (pSS) or as a (usually late) complication in patients with other rheumatic disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and scleroderma (when it is termed 'secondary' Sjögren's syndrome).

Anti-Ro and/or anti-La antibodies are found in approximately 70% of pSS patients and are associated with particular human leucocyte antigen (HLA) types — especially HLA-DR3 and, to a lesser degree, HLA-DR2. Hypergammaglobulinaemia with raised immunoglobulin G (IgG) and/or IgM concentrations is also common. Systemic features also occur in some patients with pSS.

Epidemiology, diagnosis and classification

pSS is a common disease that affects 0.1%–0.6% of the general adult population with a female to male ratio of at least 9:1 and mean age at diagnosis of approximately 50 years.[1] The revised American–European Consensus Group (AECG) criteria[2] are now the gold standard for the classification of SS and have superseded pre-existing criteria sets. They require various combinations of standardized dryness symptoms, reduction of lacrimal/salivary flow, an abnormal labial gland biopsy and/or anti-Ro/La autoantibodies (Table 1). They are also useful in clinical diagnosis.

An alternative approach to classification criteria for SS has recently been proposed by the Sjögren's International Collaborative Clinical Alliance (SICCA) Group[3] (Table 2). These criteria identify a similar cohort of patients to the AECG criteria.

Aetiology and pathogenesis

The aetiology of SS is unknown. A number of viruses, such as the Epstein–Barr virus and endogenous retroviruses, have been proposed as possible causative agents without definitive evidence. Parotid gland swelling can also be a feature of HIV infection although the histological features differ. The finding of a Sjögren-like syndrome associated with hepatitis C virus infection[4] provides some support for the hypothesis that SS could have a viral aetiology.

A number of cytokines, including interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α), IL-6, IL-10, interferon-α (IFN-α), IFN-γ and IL-18, are up-regulated in the salivary glands in pSS.[4] Chemokines such as CXCL13 and CCL21 are also expressed and may be potential therapeutic targets.[5–7] The common finding of hypergammaglobulinaemia in pSS, and the presence of autoantibodies and of B cell-containing germinal centres in salivary glands, imply a role for B cells in pSS and this is further supported by the presence of a raised serum concentration of the B cell-activating factor (BAFF), otherwise known as B cell lymphocyte stimulator (BLyS).[8,9]

IFN type I has been shown to induce BAFF expression in cultured monocytes and salivary gland epithelial cells of patients with pSS.[10] This cytokine can induce polyclonal B cell stimulation, which results in higher autoantibody production and enhanced autoantigen–autoantibody reaction with complement consumption.[10] The formation and organization of lymphocytic foci suggest an important and dynamic role for helper T cells (TH), specifically TH1, TH2 and TH17, in development of SS.[11]

Based on the findings of the genome-wide association study (GWAS) in SLE and RA, pSS is associated with a variant haplotype of STAT4.[12] STAT4 transduces IL-12, IL-23, and IFN type I in T cells and monocytes, leading to TH1 and TH17 differentiation, monocyte activation, and production of IFN-γ.[12] There is also evidence of a strong additive effect of the major risk alleles of

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Sjögren's syndrome — American–European Consensus Group criteria

- Ocular symptoms — dryness >3/12; sensation of grit; need to use tear drops
- Oral symptoms — dryness >3/12; salivary gland swelling; need for liquids to help swallowing
- Ocular signs — Schirmer ≤5 mm/5 min; Rose Bengal staining
- Histology* — labial salivary gland biopsy
- Salivary gland involvement — flow rate ≤1.5 ml/15 min; sialography; scintigraphy
- Autoantibodies* anti-Ro (SSA) &/or anti-La (SSB)

Primary SS = four out of the above six criteria with at least one of these* criteria positive *or* three out of the four objective criteria (3–6 above) *and* no exclusion criteria (sarcoid, lymphoma, hepatitis C, HIV, GvHD, head and neck radiotherapy, medications)

Secondary SS = RA/SLE, etc.: with criteria 1 and/or 2 above positive, plus two of criteria 3, 4 or 6 above

GvHD, graft-versus-host disease; HIV, human immunodeficiency virus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
See: Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria published by the American–European consensus group. *Ann Rheum Dis* 2002; **61**: 554–8.

Table 1

IRF5 and STAT4 in pSS.[13] Another gene locus in pSS is MECP2, which is critical in DNA methylation-induced transcription silencing.[14]

Although gland destruction can occur as the disease progresses, in early disease, many patients with low basal tear/saliva production remain able to produce tears/saliva on stimulation. This implies that the secretory mechanisms are intact but inhibited and antimuscarinic antibodies have been implicated.[15]

Histological features

There are three main groups of salivary glands — the parotid in front of the ears, the submandibular below the angles of the jaw and the numerous labial (lip) glands. Diagnostic labial gland biopsy is best done by an experienced specialist as there is a small chance of permanent numbness or dysaesthesia. The classical histological feature is of at least one 'focus' of 50 or more (predominantly CD4 +ve) T lymphocytes per high-powered field, clustered around a salivary duct (periductal focal lymphocytic infiltrates).

Histology reports sometimes describe a generalized scattering of inflammatory cells, including plasma cells, across the gland, described as a 'chronic sialadenitis'; this can be found in normal individuals and should be classed as a negative biopsy.

SICCA Group/American College of Rheumatology provisional classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the SICCA cohort

At least two of the following three are needed:

- Positive serum anti-Ro and/or anti-La antibodies, or positive rheumatoid factor and antinuclear antibody (titre ≥1:320)
- Presence of keratoconjunctivitis sicca (KCS) defined by an ocular staining score ≥3
- Presence of focal lymphocytic sialadenitis defined by a focus score ≥1 focus/4 mm^2 in labial salivary gland biopsy samples.

See: Shiboski SC et al. *Arthritis Care Res (Hoboken)*. 2012 April; **64**(4): 475–487.

Table 2

Clinical features

Dryness

An insidious onset of dry eyes and dry mouth is the most common presentation. Other patients may present with vaginal dryness, a dry cough or, occasionally, swollen salivary glands.

Dry eyes

Patients with mild dry eyes may self-medicate with over-the-counter lubricating eye drops. If they are referred to a hospital ophthalmology department, a slit-lamp examination of the ocular surface (including the use of vital dye eye drops) can be performed. One simple test that can be carried out in a routine clinic is Schirmer's test, using standardized blotting paper strips to measure tear flow over a 5-minute period; 5 mm or less of wetting is classed as objectively dry.

Although many patients with SS are still able to produce tears with stimulation, it is inhibition of basal tear production that makes the eyes feel dry. Some patients even complain of watery eyes resulting from chronic irritation/inflammation of the eyelid margins (blepharitis).

Not all patients with dry eyes have SS. Other causes include dysfunction of the oil-producing meibomian glands, and blockage of the lacrimal gland ductules due to mucus-producing goblet-cell injury. Hot, dry environments, air-conditioned offices, working with computers and tiredness can all cause ocular dryness symptoms. Medications such as antihistamines with anticholinergic effects reduce the neural activation of the glands and have the potential to aggravate dry eyes.

Dry mouth

The most common cause of dry mouth is medication (e.g. antidepressants, antihistamines, diuretics or beta-blockers). Head and neck radiotherapy can result in rapid and sometimes irreversible dry mouth. Diabetes mellitus or renal failure or other conditions associated with dehydration may also present with oral dryness symptoms. Some older patients have xerostomia in combination with osteoarthritis.

A number of patients who complain of oral dryness do not actually have reduced salivary flow. They perceive an alteration in oral lubrication that is often part of an oral dysaesthesia ('burning mouth syndrome'). Mouth breathing and anxiety can also cause oral dryness.

Clinical features include a lack of obvious saliva in the mouth and absence of a normal 'pool' of saliva underneath the tongue. The mucosa is dry and sticks to the gloved finger on examination. In long-standing cases, there is an increase in the incidence of dental caries and oral candidiasis may be present. In more severe cases the tongue is atrophic, fissured or even ulcerated. Unstimulated salivary flow can be measured formally by asking the patient to 'drool' into a pot for 15 min; a salivary volume of 1.5 ml or less is classed as objectively dry.