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Review Article

Sjögren's Syndrome

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Sjögren's syndrome (SS) describes xeropthalmia and xerostomia due to lymphocytic infiltrates of lacrimal and salivary glands. SS may occur alone (primary SS) or in association with several other autoimmune diseases (secondary SS). The clinical features involve a wide variety of organs, including skin, eyes, oral cavity and salivary glands, and systems, including nervous, musculoskeletal, genitourinary and vascular. Sicca symptoms can be found in a number of other disorders including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, and other rheumatic disorders.

Key Words: Sjögren, sicca, xerophtalmia, xerostomia, lacrimal

HENRIK SJÖGREN

Henrik Sjögren was born on the 23rd of July 1899 in the small Swedish town of Koping. He was the second of three children to a businessman and had a happy childhood. He attended medical school at the Karolinska Institute in Stockholm and graduated in 1927. In Karolinska Institute, he met his lifelong companion, Maria Hellgren. The couple was soon married in Paris. Sjögren's early ambition had been to become a university professor, just like his father-in-law, who was a prominent ophthalmologist in Stockholm. He then pursued training in ophthalmology at Serafimerlasarettet in Stockholm, under Professor Albin Dalen.

In January 1930, during his third year of training in ophthalmology, Sjögren encountered a 49-year-old woman with a six-year history of chronic rheumatism affecting her hands, who also complained of burning and itching, foreign body sensations and dryness of the eyes. She was unable to shed tears when crying, and later on, also developed dryness of her mouth and had trouble swallowing food without liquids. She could not dissolve a lump of sugar in her mouth. Sweating also became a problem. On physical examination, Sjögren found what was then called keratitis filiformis. He stained the eyes with fluorescein and was able to visualise epithelial defects in the lower part of the cornea. He made the observation that 1% rose bengal stained even more spots, and observed these spots by capillary microscopy. Sjögren reported this original observation and four other cases in 1930 in Hygies, the Proceedings of the Swedish Medical Association.[1]

After finishing his ophthalmology training, he moved to the Sabbatsbert City Hospital in Stockholm, and over the next three years he examined 19 patients, all women aged 29 to 72, with similar complaints. Detailed medical case histories and results of eye examination of all 19 women were included, as well as histological examinations of the conjunctiva and cornea in 12 patients and of the lacrimal glands in 10. Thirteen of the 19 patients had joint involvement, classified as deforming or non-deforming, which always began before the eye involvement became prominent. On May 8, 1933, he presented this material for his PhD thesis; Zurkenntnis der Keratoconjunctivitis Sicca.[2] His thesis described diminished tear production as the central abnormality in the eye, leading to the ulcerative lesions. He proposed the term keratoconjunctivitis, instead of filamentous keratitis, for this condition. Sjögren's former chief, the famous

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professor of pathology Folke Henschen, did not acknowledge the value of Sjögren's work and so Sjögren's thesis received the mediocre grade of 1.5 on a scale of 1 to 3, which prevented Sjögren's from being awarded the title of Docenti, a prerequisite for an academic career.

Although others had previously described the joint and ocular manifestations seen in the syndrome, the main accomplishment in Sjögren's thesis rests on the systematic and detailed description of the eye involvement. He compared the available vital staining methods with fluorescein, methylene blue and others, and proposed the use of 1% rose bengal as the best method for visualisation of corneal and conjunctival ulceration. Sjögren also used the Schirmer's test and found it not superior to the rose bengal method. In 1936, he moved from Stockholm to the city hospital of Jonkoping, where he remained as chief of ophthalmology until his retirement in 1967. During the last 20 years of his life Dr. Sjögren lived in Lund. He died in 1987 after suffering a stroke.

In the early 1940's the eponym Sjögren's syndrome began to appear in the medical literature, and his thesis was translated into English in 1943.

In 1951 Sjögren published a series with 80 patients with the syndrome, 50 of whom (62%) also had arthritis.[3] Sjögren's achievement was then recognised everywhere, and in subsequent years he was awarded honorary membership in several medical societies, including the Australian Ophthalmologic Society and the New Zealand Ophthalmological Society in 1951. In 1957 Dr Sjögren was awarded the title of "Docent" by the medical school in Gothenburg and in 1965 he was also able to fulfil his early dream of becoming a university professor when the Swedish government honoured him with the title of professor.

In 1970 Sjögren became an honorary member of the American College of Rheumatology (then called American Rheumatism Association), but it was not until 1976 that he became an honorary member of the Swedish Rheumatology Society and the Royal College of Physicians and Surgeons of Glasgow. A year before his death in 1986, he served as one of the two honorary presidents at the first International Seminar on Sjögren's syndrome.[4]

SJÖGREN'S SYNDROME

The term Sjögren's syndrome (SS) describes xeropthalmia and xerostomia due to lymphocytic infiltrates of lacrimal and salivary glands (SG) SS may occur alone (primary SS) or in association with several other autoimmune diseases (secondary SS).

CLINICAL FEATURES

SS has usually an indolent course. Patients are primarily women and the presentation is usually in the fourth or fifth decades of life. The disorder involves extra glandular sites in approximately one third of patients.[5]

CUTANEOUS LESIONS

Hypergammaglobulinaemic purpura is relatively common in SS patients and may lead to sensory peripheral neuropathy.[6] The skin lesions are non-palpable and often associated with rheumatoid factor.[7] The skin biopsies generally show ruptured blood vessels and deposition of complement.

Palpable purpura is also found in SS patients with biopsies showing leukocytoclastic vasculitis,[8] and it may be associated with central nervous system or pulmonary involvement.[9,10]

Asymmetric vasculitic skin lesions in SS patients may accompany mononeuritis multiplex.[11] Additional cutaneous features include sub-cutaneous amyloid and anetoderma.[12,13] Among Japanese SS patients, annular erythema has been reported in a relatively high proportion of patients.[14] Urticarial vasculitis has been reported in association with SS.[15] Dryness of the skin in some patients has been associated with lymphocytic infiltrates in the eccrine glands.[16]

OCULAR LESIONS

Xerophthalmia (dryness of eyes) is a major manifestation of SS. Diminished secretion of tears leads to destruction of the corneal and bulbar conjunctival epithelium (keratoconjunctivitis sicca)

(KCS). Symptoms of KCS are a sandy feeling, itchiness, burning sensation, and inability to tolerate smoke and light. Clinical signs are dilatation of the bulbar conjunctival vessels, pericorneal injection, and irregularity of the corneal image.

ORAL MANIFESTATIONS

Xerostomia is the predominant oral symptom of SS resulting in sore mouth, and trouble in chewing and swallowing. Oral candidiasis has been reported to occur in up to 80 percent of patients with SS. This usually takes the form of angular cheilitis and acute erythematous candidiasis.[17] Major SG enlargement, particularly the parotid glands, occurs in 25 to 66 percent of patients with primary SS, but is uncommon in secondary SS5. Dental decay is a common complication and caries risk is increased in SS patients.[18]

In addition to subjective symptoms of dryness, decrease in mucin production predisposes the patients to loss of taste, bacterial and yeast infection, and increased predisposition to caries.[19]

VASCULAR INVOLVEMENT

Raynaud's phenomenon is found in more than one third of patients with primary SS.[20] Deep vein thrombosis may occur in SS patients and should stimulate the search for anticardiolipin antibodies. Vasculitis of the skin is most common, presenting with palpable purpura. Other sites that might be involved with vasculitis include bladder (interstitial cystitis), kidney and lung. Abdominal and mesenteric vasculitis may occur, most commonly in patients with mixed cryoglobulinaemia.[21]

MUSCULOSKELETAL MANIFESTATIONS

SS is usually confined to exocrine glands with only mild rheumatic complaints. However, fatigue, general malaise, low-grade fever, myalgia, and arthralgia may occur in patients with SS. Jaccoud's arthropathy may follow transient episodes of lupus-like non-erosive arthritis.

URINARY TRACT ABNORMALITIES

Urinary acidification test result is abnormal in about one third of patients with SS. Most of these patients have distal renal tubular acidosis. Nephritis is generally interstitial, but glomerulonephritis may occur in primary SS patients. Membranous or membranoproliferative, immune complex glomerulonephritis associated with cryoglobulinaemia may rarely occur.[22]

NEUROPSYCHIATRIC INVOLVEMENT

Peripheral sensory or sensory-motor neuropathy or mononeuritis multiplex occurs in approximately 10 to 20 percent of patients with primary SS. Carpal tunnel syndrome and cranial neuropathy may occasionally occur.[23] Hemiparesis, seizures, cerebellar defects, and transverse myelitis have been described in a few patients. Anxiety, depression, and personality disorders are common.[24]

OTHER MANIFESTATIONS

Dry cough due to dryness of tracheobronchial mucosa (xerotrachea) and dyspnoea due to interstitial lung disease may occur.[25] Patients with SS have a high prevalence of sensorineural hair loss.[26]

Dryness of pharynx and oesophagus may cause dysphagia. Liver involvement is rare in primary SS. It may present with elevated liver enzymes or in the presence of antimitochondrial antibodies. Liver biopsy shows features of early primary biliary cirrhosis.[27]

Patients with SS are at increased risk of developing non-Hodgkin's lymphoma. These lymphomas are primarily of B cell origin.[28]

Neonatal lupus may be found in the children of mothers with SS, SLE, and in a proportion of mothers bearing antibodies against SS-A and SS-B antigens but lacking clinical SS.[29]

SECONDARY SJÖGREN'S SYNDROME

Sicca symptoms can be found in a number of other disorders including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, and other rheumatic disorders.[5] Five percent of patients with rheumatoid arthritis have clinically overt SS, whereas 20% have sub-clinical SS.[30] KCS is the predominant manifestation of secondary SS while xerostomia and other manifestations are uncommon in secondary SS.

PATHOGENESIS

Critical features of the pathogenesis include: (1) failure to remove autoimmune T-cells at the level of thymic selection, (2) aberrant expression of increased levels of cell adhesive molecules on glandular epithelial cells resulting in infiltration of auto-immune lymphocytes to glands, (3) up-regulation of HLA-DR, (4) polyclonal activation of B-lymphocytes, (5) secretion of pro-inflammatory cytokines by both lymphocytes and epithelial cells, (6) decreased secretion by the residual glandular acini, and (7) resistance of T-cells within the gland to undergo apoptosis.[31]

Much evidence now exists that antibodies found in SS are the result of immune responses to antigens generated by apoptosis.[32] There is greater expression of pro-apoptotic molecules (CD95/Fas, Bax) in acinar and ductal epithelial cells than of the anti-apoptotic proteins Bcl-2 and Bcl-X.[33,34] Aberrant over-expression of bcl-2 in the lymphocytes of SS patients also suggests a potential role in B-cell lymphoproliferation and the propensity of these patients to develop lymphoma.

Glandular acinar and ductal cells secrete water, proteins, and mucopolysaccharides in response to neural stimulation through muscarinic M3 receptors and vasoactive intestinal peptide (VIP) receptors.[35] This complex mixture forms a hydrated gel that lubricates the ocular surface (i.e., tears) and the oral mucosa (i.e., saliva). In SS, the lacrimal or SG is incapable of adequate response to neural signals as a consequence of local immune infiltrates and their derived cytokines.[36]

Evidence to incriminate an infectious agent in the pathogenesis of SS remains unproven. Antibody titres to a variety of Epstein-Barr virus (EBV) antigens have been reported to be elevated in SS patients.[37]

INVESTIGATIONS

Mild normochromic, normocytic anaemia is common. Elevated ESR is found in 70 percent of patients. C-reactive protein concentrations are usually normal in primary SS, but may be elevated in secondary SS.

Profound hypergammaglobulinaemia, circulating immune complexes, and multiple autoantibodies directed against both organ and non-organ specific auto-antigens are due to polyclonal B-cell hyper-reactivity. Polyclonal activation of gammaglobulins can evolve to polyclonal-oligoclonal-monoclonal activation, and can end up as malignant monoclonal proliferation. One third of patients with SS have high serum levels of mixed monoclonal cryoglobulins (type II) and the occurrence of cryoglobulinaemia correlates with a high prevalence of extra-glandular disease and autoantibodies to Ro (SSA), as well as with a higher risk for the development of lymphoma.[38]

Organ specific autoantibodies described in SS include antibodies to various cellular antigens of salivary ducts, thyroid, gastric mucosa, erythrocytes, pancreas, prostate, and nerve cells. High titres of non-organ specific autoantibodies are found in 70 percent of patients and include rheumatoid factor, anti-histone, and antibodies to antinuclear, anti-centromere, anti-mitochondrial, anti-cytokeratin, anti-single-stranded DNA, and nRNP[39,40].

Anti-Ro (SSA) and anti-La (SSB) antibodies are found in approximately 95 percent and 87 percent of primary SS patients, respectively.[41] These autoantibodies are associated with earlier onset and longer duration of disease and the recurrence of parotid gland enlargement, splenomegaly, lymphadenopathy, and vasculitis.[42]

Antineutrophil cytoplasmic antibodies (ANCA) are relatively uncommon in patients with primary SS, and when present they are usually p-ANCA (perinuclear) antibodies. Caution must be used in

interpreting the ANCA in SS patients as false-positive findings may result from the presence of other anti-nuclear antibodies.[43] Antibodies against endothelial cells have been found in a subset of SS patients, but they are also detected in many other autoimmune disorders and are not closely associated with skin vasculitis.[44] Anticardiolipin antibodies are found in a subset of SS patients and are generally IgA isotype.[45] Antibodies against muscarinic M3 receptors have been found in SS patients and may compete with acetylcholine.

DIAGNOSIS

There is no uniformly agreed criterion for the diagnosis of SS. The demonstration of focal lymphocytic infiltrates on minor SG biopsy has remained the gold standard for the oral component of SS. A cluster of 50 or more lymphocytes is called a "focus" and an average focus score of 2 or more per 4 mm^2 fulfils the diagnosis of SS in the San Francisco criteria[46] (Table 1). Another classification system is the San Diego criteria where patients have, (a) objective KCS and xerostomia, and (b) a characteristic minor SG biopsy or evidence of a systemic autoimmune disease as manifested by characteristic autoantibodies[47] (Table 2). Recently a revised version of the European criteria proposed by the American-European Consensus Group has been published[48] (Table 3). It defines the rules for classifying patients with primary or secondary SS more clearly (Table 4) and provides more definite exclusion criteria (Table 5).

TREATMENT

There is no cure for SS at present. Treatment is, therefore, directed at relief of symptoms. For dry eyes, the initial therapy is the administration of artificial tears on a regular basis. Avoidance of windy and dry climates, in preference to living in environments with low levels of humidity, dust, or smoke is helpful. In patients with inadequate response to artificial tears, punctal occlusion to decrease the drainage of tears may help. Muscarinic agonists (pilocarpine and cevimeline) may be used for treatment of dry mouth and eyes. The presence of low-grade oral candida can greatly contribute to oral discomfort. This condition is treated with topical clotrimazole and oral nystatin. Amphotericin B lozenges can be used in refractory

Table 1. San Francisco Criteria for Primary and Secondary SS

Primary SS
1. Focal lymphocytic sialadenitis in minor SG biopsy with focus score >1 focus/4 mm^2 or benign lymphoepithelial lesion in major SG, and
2. KCS
   a. Characteristic corneal and conjunctival epithelial staining with rose bengal, seen through a slit-lamp, and
   b. Reduced tear meniscus and break-up time, or
   c. Schirmer's test result (without anaesthesia) $\leq$ 5 mm/5 minutes

Secondary SS
1. Rheumatoid arthritis or other connective tissue disease diagnosed by established criteria, and
2. One or both of the criteria for primary SS described above

Possible SS
1) One component of primary SS described above, and
2) Presence of any of the following:
   Pulmonary lymphocytic interstitial infiltrates
   Interstitial nephritis and/or renal tubular acidosis
   Purpura (with hypergammaglobulinaemia or vasculitis)
   Chronic liver disease (not cirrhosis or infectious)
   Peripheral neuropathy
   Hypergammaglobulinaemia (poly- or monoclonal) with anti-Ro/SS-A and/or anti-La/SS-B

Table 2. San Diego Criteria for SS

1. Objective evidence of KCS, as documented by rose bengal or fluorescein dye staining
2. Objective evidence of diminished SG flow
3. Minor SG biopsy, obtained through normal mucosa, with the specimen containing at least 4 evaluable gland lobules and having an average of at least 2 foci/4 mm^2
4. Evidence of a systemic autoimmune response, as manifested by the presence of autoantibodies, such as rheumatoid factor and/or antinuclear antibody.

Definite SS: When all 4 criteria are met.
Possible SS: When 3 criteria are present.
Specific exclusions for the diagnosis of SS are pre-existing lymphoma, graft-versus-host disease, sarcoidosis, and acquired immunodeficiency disease.

Table 3. Revised International Classification Criteria for SS

I- Ocular symptoms: a positive response to at least one of the following questions: i. Have you had daily, persistent, troublesome dry eyes for more than three months? ii. Do you have a recurrent sensation of sand or gravel in the eyes? iii. Do you use tear substitutes more than three times a day?
II- Oral symptoms: a positive response to at least one of the following questions: i. Have you had a daily feeling of dry mouth for more than three months? ii. Have you had recurrently or persistently swollen salivary glands as an adult? iii. Do you frequently drink liquids to aid in swallowing dry food?
III- Ocular signs: a positive result for at least one of the following two tests: i. Schirmer's test, performed without anaesthesia ($\leq$ 5 mm in 5 min) ii. Rose bengal score or other ocular dye score ($\geq$ 4 according to Bijsterveld's scoring system)
IV- Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score $\geq$ 1, defined as the number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.
V- Salivary gland involvement: a positive result for at least one of the following diagnostic tests: i. Unstimulated whole salivary flow ($\leq$ 1.5 ml in 15 min) ii. Parotid sialography showing the presence of diffuse sialectasis (punctate activity or destructive pattern), without evidence of obstruction in the major ducts iii. Salivary scintigraphy showing delayed uptake, reduced concentration and /or delayed excretion of tracer
VI- Autoantibodies: presence in the serum of antibodies to Ro (SSA) or La (SSB) antigens or both

Table 4. Revised Rules for Classification of SS

For primary SS In patients without any potentially associated disease, primary SS may be defined as follows: i. The presence of any 4 of the 6 items that are indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive ii. The presence of any 3 of the 4 objective criteria items (items III, IV, V, VI)
For secondary SS In patients with a potentially associated disease, the presence of items I or II plus any 2 from among items III, IV and V, may be considered indicative of secondary SS

Table 5. Exclusion Criteria for SS

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

cases.[49] Careful attention to dental hygiene, avoidance of sugar-containing food, and the use of topical fluorides may help retard decay and periodontal disease. Propionic acid gels may be used to treat vaginal dryness.

Parotid or submandibular swelling is a relatively common problem in SS patients. The prompt use of antibiotics (and occasionally low dose steroids) to help reduce the inflammation will help prevent problems of glandular abscess. Persistent swelling requires further imaging studies to rule out tumour or calculus.

The treatment of the extra glandular symptoms of SS is similar to that of SLE.[50] Symptoms of arthralgia may respond to non-steroidal, anti-inflammatory agents or antimalarials.[51] In SS patients resistant to NSAIDs, low-dose methotrexate may be useful to control arthralgia and myalgia.[52] Systemic corticosteroids are given for more serious extra-glandular complications, diffuse interstitial lung disease, glomerulonephritis or vasculitis. The treatment of leukocytoclastic vasculitis needs to be more aggressive and may require higher-dose corticosteroids or even cyclophosphamide.

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