Sjögren’s Syndrome: A Review

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INTRODUCTION

Sjögren’s syndrome is a chronic, systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. Involvement of the lacrimal and salivary glands eventually leads to two typical features of the disease: Keratoconjunctivitis sicca and xerostomia. It is named after Swedish ophthalmologist Henrik Sjögren (1899-1986) who first described it. Sjögren’s syndrome (SS) may occur in two forms: Primary Sjögren syndrome (PSS), when the clinical manifestations of the syndrome are seen alone, and secondary Sjögren syndrome (SSS), when associated with another autoimmune disease, most commonly rheumatoid arthritis, systemic sclerosis, primary biliary cirrhosis or Hashimoto thyroiditis (associated Sjögren syndrome). Hallmarks are the dry mouth and dry eyes known as the Sicca syndrome. Sjögren syndrome affects 1 million to 4 million people in the United States. Most are over 40 years old at the time of diagnosis. As there is no known cure for Sjögren syndrome, treatment focuses on relieving symptoms and preventing complications. The most serious complication associated with primary Sjögren’s syndrome is the development of a lymphoproliferative disease, primarily non-Hodgkin lymphoma.

Numerous criteria have been proposed to facilitate the accurate classification and diagnosis of Sjögren’s syndrome in adults. The most inclusive, well-defined and widely used criteria are those developed and validated between 1989 and 1996 by the American-European Consensus Group. International classification criteria for Sjögren’s syndrome. This set of criteria include six different items:

1. Ocular symptoms (at least one of the following symptoms): Daily, persistent, troublesome dry eyes for more than three months, recurrent sensation of sand or gravel in the eyes, use of tear substitutes more than three times per day.
2. Oral symptoms (at least one of the following symptoms): Daily feeling of dry mouth for more than three months, recurrent or persistently swollen salivary glands as an adult need to drink liquids frequently to aid in swallowing dry food.
3. Ocular signs (positive results from at least one of the following tests): Schirmer’s test, Rose bengal test or other ocular dye test.
4. Histopathology (positive biopsy of a salivary gland)
5. Salivary gland involvement (positive results from at least one of the following tests): Unstimulated whole salivary flow collection (less than 1.5 ml in 15 minutes), parotid sialography showing the presence of diffuse sialectasia, and delayed excretion of tracer.

Sjögren’s syndrome is rare in children and adolescents. This fact coupled with additional diagnostic difficulties specific to this subset of patients, such as difficulty in obtaining reliable history data and diversity of clinical presentation accounts for higher frequency of underdiagnosed cases compared with adult cases. No universal diagnostic criteria for Sjögren’s syndrome in children have been accepted. Therefore, the above-mentioned widely accepted modified European criteria for adults are currently the most valuable criteria for pediatric patients.

PREVALENCE

It has been estimated that up to 4 million Americans are afflicted with Sjögren’s syndrome and that 1 to 2% of the population in the United States has been diagnosed with Sjögren’s syndrome. However, the disorder may be difficult to diagnose because the incidence of the disease may be considerably higher. Sjögren’s syndrome is a condition that affects primarily women with a female to male ratio of about 24:1, meaning that about 95% of people who suffer from Sjögren’s syndrome are women. Symptoms of the disorder most often begin between the ages of 40 to 60 predominantly in peri/postmenopausal women, but are also seen in young women in their 20s and 30s. The average age of onset is 52 years old. The overall prevalence of Sjögren’s syndrome in the general population has been estimated to range from 0.5 to 3.0%.

PATHOGENESIS

The pathogenesis of Sjögren’s syndrome is obscure. It is probably the result of an environmental stimulus that promotes an autoimmune reaction in genetically susceptible persons. Infectious
agents—most commonly sialotropic viruses—have been postulated to trigger the syndrome; however, associations with most of the potential viral candidates, including cytomegalovirus and Epstein-Barr virus, are weak.\(^5\) Serologic studies show an association between primary Sjögren’s syndrome and HLA-DR haplotypes.\(^6\) Sjögren’s syndrome represents a complex, multifaceted activation of the immune system. B-lymphocyte dysregulation and hyperactivity play a major role in the disease. The histological hallmark of Sjögren’s syndrome is lymphocytic infiltration of the exocrine glands, which leads to acinar gland degeneration, necrosis, atrophy and decreasing lacrimalisalivary function.\(^7\) Glandular neurodegeneration is also present, which may explain why patients experience sicca syndrome when more than 50% of the glandular epithelial cells remain intact.\(^8\)

### CLINICAL FEATURES

The hallmark symptoms of the disorder are dry eyes and dry mouth, also referred to as xerophthalmia (or keratoconjunctivitis sicca (KCS) and xerostomia respectively). Eye symptoms include dryness, grittiness, pruritus and foreign body sensation. Lack of tears can cause permanent eye damage. Oral symptoms include difficulty in speaking, eating or swallowing, and frequent sips of water may be needed. On physical examination, the patient’s eye may show conjunctival infection because there may be ocular inflammation independent of lacrimal gland involvement. In more severe cases, clouding of the cornea may be seen.\(^9\) Early oral findings include decreased salivary pool and dry mucous membranes which can progress to erythema, fissuring and ulceration.\(^9\) Insufficient saliva can cause cavities dull taste and make eating and swallowing painful. Dryness of the trachea can result in cough. Parotid glands may be tender or swollen. Patients also may present with extraglandular symptoms (Table 1).

### DIAGNOSIS

The diagnosis of primary Sjögren’s syndrome is strongly suggested in patients who present with signs and symptoms of oral and ocular dryness and who test positive for antibodies to the anti-SS-A or anti-SS-B antigen or who have a positive salivary gland biopsy.\(^9\) Sjögren syndrome often has an insidious onset, a variable course, and a wide spectrum of clinical manifestations, making the diagnosis difficult or delayed.\(^9,13\) Early recognition of Sjögren syndrome may prevent complications, such as dental caries, corneal ulceration, chronic oral infection and sialadenitis, and it allows for clinical surveillance for the development of serious extraglandular systemic manifestations.\(^13\) Aside from xerostomia and KCS, which are nonspecific, Sjögren syndrome lacks a single distinguishing feature and is identified by a combination of clinical manifestations and laboratory findings.\(^14\) The most recent criteria for classification of Sjögren syndrome requires a positive minor salivary gland biopsy or a positive anti-SS-A or anti-SS-B antigen test.\(^15\)

Although the diagnosis of Sjögren syndrome may be suggested by the patient’s history and physical examination, there are multiple objective tests to help with the diagnosis. These tests are not commonly performed in the family physician’s office.

Eye symptoms are usually evaluated with the Schirmer’s test or the rose bengal test. The Schirmer test involves placing a sterile filter paper strip beneath the lower eyelid for five minutes. If the moistened area measures < 5 mm, the test is positive.\(^9\) The rose bengal test usually is performed by an ophthalmologist; 1% rose bengal dye is instilled and the ocular surface integrity is evaluated by quantitatively scoring the staining of the conjunctiva.\(^16\) Rose bengal dye will stain devitalized corneal and conjunctival epithelial cells. The test will identify KCS when minimal ocular symptoms are present.\(^12\) A routine slit-lamp evaluation can identify a diminished tear meniscus.\(^12\)

Oral dryness can be evaluated objectively by nonstimulated whole saliva flow collection, in which the patient spits into a graduated test tube every minute for 15 minutes. Collection of < 1.5 ml in 15 minutes is considered a positive result.\(^14\) Other tests include contrast sialography, which visualizes the salivary glands and ducts via contrast dye injection into the Stensen duct and scintigraphy, which evaluates salivary gland function by measuring sequential uptake and excretion of technetium. Although once considered the gold standard for diagnosis of Sjögren syndrome, minor salivary gland biopsy of tissue taken from the patient’s lip is not always necessary.\(^13\) A positive biopsy is defined as at least one focus of dense, inflammatory infiltrate containing at least 50 lymphocytes per 4 mm.\(^9,12\) The lip biopsy may be useful in ambiguous cases or when therapy beyond symptom management is being considered.

Blood tests can be done to determine if a patient has high levels of antibodies that are indicative of the condition, such as antinuclear antibody (ANA) and rheumatoid factor (because SS frequently occurs secondary to rheumatoid arthritis), which are associated with autoimmune diseases. Typical Sjögren’s syndrome ANA patterns are SSA/Ro and SSB/La, of which SSB/La is far more specific; SSA/Ro is associated with numerous other autoimmune conditions but are often present in Sjögren’s Syndrome.\(^17,18\)

Ultrasound examination of the salivary glands is the simplest confirmatory test and has the added advantage of being noninvasive with no complications. The parenchyma of the gland demonstrates multiple, small, 2 to 6 mm hypoechoic lesions which are representations of the lymphocytic infiltrates. Often sialodacys with calculi are demonstrated if the disease is advanced. The sonographic findings have excellent symptom correlation. The other advantage of ultrasound is that complications of the disease, such as extranodal lymphomas can often be detected as larger 1 to 4 cm hypoechoic intraparenchymal masses.
A radiological procedure can also be used as a reliable and accurate way of diagnosing Sjögren’s syndrome. A contrast agent is injected into the parotid duct (of Stensen), which is a duct opening from the cheek into the vestibule of the mouth opposite the neck of the upper second molar tooth. Widespread puddling of the injected contrast scattered throughout the gland indicates Sjögren’s syndrome.

**TREATMENT**

Because there is no known cure for Sjögren’s syndrome, treatment focuses on relieving symptoms and preventing complications. Treatments can be grouped into regimens for KCS, xerostomia and systemic manifestations.

**Xerophthalmia**

There is neither a known cure for Sjögren’s syndrome nor a specific treatment to permanently restore gland secretion. Instead, treatment is generally symptomatic and supportive. Moisture replacement therapies, such as artificial tears, may ease the symptoms of dry eyes. Development of a solution that completely simulates human tears with all of their complex constituents, has not yet been achieved. Preservative-free artificial tears are tolerated better than solutions with preservatives. If artificial tears do not satisfactorily relieve symptoms, the next step is increasing tear production by stimulating muscarinic receptors which are a type of cholinergic receptor found on exocrine glands, heart muscle and smooth muscle.

Several randomized trials have shown two muscarinic agonists, pilocarpine (Salagen) and cevimeline (Evoxac), to be effective. Pilocarpine is a nonselective muscarinic agonist, whereas cevimeline is a selective muscarinic agonist that reportedly has less effect on cardiac and lung tissues. Oral pilocarpine, at a dosage of 5 mg twice daily, has been shown in a small randomized control trial (RCT) to decrease subjective eye symptoms and improve results of rose bengal testing. Oral cevimeline, at a dosage of 30 mg three times daily, relieved subjective eye symptoms in another small RCT. Muscarinic agonists are contraindicated in angle-closure glaucoma and uncontrolled asthma. Other topical anti-inflammatory medications, such as steroids and cyclosporine (Neoral), are of questionable benefit.

Punctal plugs can be inserted to help retain tears on the ocular surface for a longer time. Each eye has two sites at the inner corner of each eyelid where tears drain from the eye. The upper eyelid ‘puncta’ drains approximately 40% of your tears away and the lower puncta drains away the remaining 60% of your tears. If there is a problem with the quantity of your tears, as there is in Sjögren’s disease, plugging the lower puncta can result in the tears that you have remaining on the eye longer.

Punctal plugs can be inserted into the lower or upper tear drainage canals of the eyes. The procedure takes only a few minutes and is painless. It can be done in the optometrist or ophthalmologist’s office. Generally, collagen plugs are inserted first. These plugs will dissolve within a few days, so it gives the patient a chance to see if there is any improvement in comfort. Generally, the improvement is immediate. If you wish to proceed with permanent plugs you may, although these too can be removed, if necessary.

**Xerostomia**

Treatment for xerostomia consists of good oral hygiene, salivary stimulation, use of saliva substitutes and recognition of complications. Preventive dental treatment is also necessary (and often overlooked by the patient), as the lack of saliva associated with xerostomia (dry mouth) creates an ideal environment for the proliferation of bacteria that cause dental caries (cavities).

Daily topical fluoride use and antimicrobial mouth rinses can help to prevent caries in patients with reduced salivary flow. Sugar free chewing gums and sour lemon lozenges may be used for salivary stimulation. Xylitol, a naturally occurring sugar substitute, has been shown to decrease dental caries when used in chewing gum in the general population. Several over-the-counter salivary substitutes are available as lozenges, rinses, sprays and swabs. They contain carboxymethylcellulose, mucin or glycerine, which help to lubricate the oral mucosa. Muscarinic agonists also may be used.

Existing cavities must also be treated, as cavities that extend into the tooth cannot be effectively treated through teeth cleaning alone, and are at a high risk of spreading into the pulp of the tooth, leading to the loss of vitality and need for extraction or root canal therapy. This treatment regimen is the same as that used for all xerostomia patients, such as those undergoing head and neck radiation therapy which often damages the salivary glands, as they are more susceptible to radiation than other body tissues.

Unfortunately, many patients, not realizing the need for dental treatment, do not see a dentist until most of their teeth are beyond the point of restoration. It is not uncommon for a dentist to see a xerostomia patient with severe, untreatable caries in almost every tooth. In such cases, the only treatment is to extract all of the patient’s teeth and fit the dentures.

**Systemic Symptoms**

Antimalarial medications and corticosteroids are being reevaluated in the treatment of Sjögren’s syndrome. Hydroxychloroquine (Plaquenil) may be useful for treating the arthralgias and fatigue associated with Sjögren syndrome. Rituximab (Rituxan), an anti-CD20 monoclonal antibody that depletes B-lymphocytes, holds promise as a therapy for severe inflammatory manifestations of Sjögren syndrome.

**PROGNOSIS**

Sjögren’s syndrome can damage vital organs of the body with symptoms that may plateau or worsen, but the disease does not go into remission as with other autoimmune diseases. Some people may experience only the mild symptoms of dry eyes and mouth, while others have symptoms of severe disease. Many patients are able to treat problems symptomatically. Others are forced to cope with blurred vision, constant eye discomfort, recurrent mouth infections, swollen parotid glands, hoarseness and difficulty in swallowing and eating. Debilitating fatigue and joint pain can seriously impair quality of life. Some patients can develop renal involvement (autoimmune tubulointerstitial nephritis) leading to proteinuria, urinary concentrating defect and distal renal tubular acidosis.

Patients with Sjögren’s syndrome have a higher rate of non-Hodgkin lymphoma compared to both patients with other autoimmune diseases and healthy people. About 5% of patients with Sjögren’s syndrome will develop some form of lymphoid malignancy. Patients with severe cases are much more likely to develop lymphomas than patients with mild or moderate cases. The most common lymphomas are salivary extranodal marginal lymphomas.
zone B-cell lymphomas (MALT lymphomas in the salivary glands)\textsuperscript{26} and diffuse large B-cell lymphoma.\textsuperscript{27}

REFERENCES


