Diagnosis and Management of Sjögren Syndrome

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Sjögren syndrome is a systemic autoimmune disease characterized by dry eyes and dry mouth. Other organ systems are affected in many patients. Sjögren syndrome is classified as primary or secondary. In primary disease, Sjögren syndrome is a solitary process, whereas secondary disease accompanies another autoimmune disease—often rheumatoid arthritis. Sjögren syndrome is a challenging diagnosis, requiring the family physician to coordinate with a team of specialists, including dentists, otolaryngologists, rheumatologists, and ophthalmologists. Pilocarpine and cevimeline can help relieve dry eyes and dry mouth. (*Am Fam Physician*. 2009;79(6):465-470, 472. Copyright © 2009 American Academy of Family Physicians.)

▶ **Patient information:** A handout on Sjögren syndrome, written by the authors of this article, is provided on page 472.

Sjögren syndrome is one of the three most common systemic autoimmune diseases.[1] As many as 1 to 2 million persons in the United states are affected[2]; the reported prevalence is between 0.05 and 4.8 percent of the population.[3] A study from Olmsted County, Minn., estimated the incidence of physician-diagnosed primary Sjögren syndrome to be about four cases per 100,000 persons.[3]

Primary Sjögren syndrome mainly affects middle-age women. In a cohort of 400 persons with Sjögren syndrome, 93 percent were women, and the mean age at onset of symptoms was 52.7 years.[4]

Pathogenesis

The pathogenesis of Sjögren syndrome is obscure.[1] 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 syndrome and HLA-DR haplotypes.[6]

Sjögren 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 syndrome is lymphocytic infiltration of the exocrine glands, which leads to acinar gland degeneration, necrosis, atrophy, and decreasing lacrimosalivary function.[7] Glandular neurodegeneration is also present, which may explain why patients experience sicca syndrome when more than 50 percent of the glandular epithelial cells remain intact.[8]

Typical Presentation

Sjögren syndrome typically presents as dry eyes and dry mouth, also referred to as xerophthalmia (or keratoconjunctivitis sicca [KCS]) and xerostomia, respectively. In a large prospective cohort study of 400 patients with Sjögren syndrome, 98 percent presented with xerostomia, and 93 percent with xerophthalmia.[4] Eye symptoms include dryness, grittiness, pruritus, and foreign body sensation. Oral symptoms include difficulty speaking, eating, or swallowing, and frequent sips of water may be needed.

On physical examination, the patient's eye may show conjunctival injection 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] The patient may also have multiple dental caries as a result of decreased

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SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
The muscarinic agonists pilocarpine (Salagen) and cevimeline (Evoxac) can be used to relieve xerophthalmia in patients with Sjögren syndrome.	B	21, 22
Muscarinic agonists improve subjective and objective signs and symptoms of xerostomia in patients with Sjögren syndrome.	B	25, 26
Interferon alfa improves subjective oral and ocular dryness and increases nonstimulated saliva flow in patients with Sjögren syndrome.	B	7

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

salivary flow; saliva prevents dental caries by promoting dental remineralization, providing antimicrobial activity against cariogenic bacteria, and maintaining a physiologic oral pH level.[10] Parotid glands may be tender or swollen. Other causes of enlarged parotid glands include acute suppurative sialadenitis, mumps, tuberculosis, sarcoidosis, and lymphoma.[11]

Patients also may present with extraglandular symptoms *(Table 1)*.[4,12]

Diagnosis

The diagnosis of primary Sjögren 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.[1] *Table 2* lists the frequency of positive results for common laboratory tests in Sjögren syndrome.[2-4,9] It should be noted that antibodies to the anti-SS-A and anti-SS-B antigens are not specific to Sjögren syndrome; they may be present in persons with other diseases (e.g., lupus) and in healthy persons.

Sjögren syndrome often has an insidious onset, a variable course, and a wide spectrum of clinical manifestations, making the diagnosis difficult or delayed.[2,13] 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 *(Table 3)*.[15] These criteria were not designed for diagnosis, but for establishing homogeneity of research cohorts. However, they provide a useful framework to make a diagnosis.

Table 4 lists the differential diagnosis of xerophthalmia and xerostomia, and their distinguishing clinical features.[1,9,10,16-18]

DIAGNOSTIC TESTING

Although the diagnosis of Sjögren syndrome may be suggested by the patient history and

Table 1. Extraglandular Manifestations of Sjögren Syndrome

Clinical signs and symptoms	*Frequency (%)*
Arthralgia or nonerosive arthritis characterized by tenderness, swelling, or effusion of peripheral joints	37 to 75
Gastrointestinal symptoms (reflux, dyspepsia, diarrhea, constipation)	54
Autoimmune thyroiditis	15 to 33
Pulmonary disease (chronic cough, recurrent bronchitis with chronic diffuse interstitial infiltrates on radiography, abnormal spirometry, pulmonary alveolitis or fibrosis on computed tomography)	29
Raynaud's phenomenon	16 to 28
Cutaneous vasculitis	12
Peripheral neuropathy	7
Lymphadenopathy (enlarged lymph nodes in cervical, axillary, or inguinal region)	7
Renal involvement (proteinuria, renal tubular acidosis, interstitial nephritis, glomerulonephritis, abnormal urinalysis)	6
Fever not associated with infectious process	6

Information from references 4 and 12.

Table 2. Frequency of Positive Laboratory Test Results in Primary Sjögren Syndrome

Tests	*Frequency (%)*
Antinuclear anitbody	55 to 97
Anti-SSA (Ro)	16 to 70
Anti-SSB (La)	7 to 50
Rheumatoid factor	32 to 90

Information from references 2 through 4, and 9.

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 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 less than 5 mm, the test is positive.[2] 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.[19] Rose bengal dye will stain devitalized corneal and conjunctival epithelial cells. The test will identify KCS when minimal ocular symptoms are present.[9] A routine slit-lamp evaluation can identify a diminished tear meniscus.[9]

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 less than 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 99m.[10]

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^2.[9] The lip biopsy may be useful in ambiguous cases or when therapy beyond symptom management is being considered.

Treatment

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

XEROPHTHALMIA

Ocular treatment begins with topical tear replacement. Development of a solution that completely simulates human tears, with all of their complex constituents, has not yet been achieved.[20] 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

Table 3. Revised International Classification Criteria for Sjögren Syndrome

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 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
   - Salivary scintigraphy showing delayed uptake, reduced concentration, and delayed excretion of tracer
6. Presence of antibodies to anti-SS-A and anti-SS-B antigens

NOTE: *The classification requires four of the six items, one of which must be a positive minor salivary gland biopsy or a positive antibody test, or the presence of three of the four objective items (items 3, 4, 5, and 6).*

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Table 4. Differential Diagnosis of Dry Eyes and Dry Mouth

Condition	*Comment*
Causes of dry eyes	
Allergic conjunctivitis	Burning eyes, mucoid secretion, and conjunctival erythema
Blepharitis	Eyelid margins are erythematous and thickened with crusts and debris within the lashes; usually worse in the morning and improves as the day goes on; does not respond to lubricant drops
Environment	Dryness caused by prolonged exposure to low humidity, dust, or sun
Lifestyle	Dryness caused by diminished blinking during long periods of reading, driving, or computer use
Medications	Diuretics and anticholinergic medications, including treatments for Parkinson disease, Alzheimer disease, depression, allergic rhinitis, and incontinence
Rosacea	Ocular symptoms (e.g., itchy, burning, dry eyes with eyelid swelling and erythema) occur in 50 percent of patients with rosacea
Causes of dry mouth	
Diabetes	Dryness worsens with poor glycemic control
Head and neck radiation	External beam radiation damages salivary glands
Hepatitis C	Sialadenitis results in dry mouth in 15 percent of persons with hepatitis C
HIV infection	HIV-related salivary gland disease exhibits clinical manifestations similar to Sjögren syndrome
Medications	Diuretics and anticholinergic medications, including treatments for Parkinson disease, Alzheimer disease, depression, allergic rhinitis, and incontinence
Obstructed nasal passages	Dryness caused by mouth breathing
Sarcoidosis	Decreased salivary flow results from noncaseating granulomas in salivary glands

HIV = human immunodeficiency virus.

Information from references 1, 9, 10, and 16 through 18.

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.[21,22] Pilocarpine is a nonselective muscarinic agonist, whereas cevimeline is a selective muscarinic agonist that reportedly has less effect on cardiac and lung tissues.[23] 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.[21] Oral cevimeline, at a dosage of 30 mg three times daily, relieved subjective eye symptoms in another small RCT.[22] 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.[20]

XEROSTOMIA

Treatment for xerostomia consists of good oral hygiene, salivary stimulation, use of saliva substitutes, and recognition of complications. Xerostomia increases the risk for dental caries and oral infections. Daily topical fluoride use and antimicrobial mouth rinses can help prevent caries in patients with reduced salivary flow.[23] 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.[24] Several over-the-counter salivary substitutes are available as lozenges, rinses, sprays, and swabs. They contain carboxymethylcellulose, mucin, or glycerine, which help lubricate the oral mucosa. Muscarinic agonists also may be used. An RCT of 44 patients showed that pilocarpine at a dosage of 5 mg four times daily is superior to placebo in improving subjective xerostomia.[25] Another small RCT showed that cevimeline at a dosage of 30 mg three times daily improves xerostomia symptoms and salivary flow.[26]

Although pilocarpine and cevimeline have been shown to reduce symptomatic oral dryness and to produce transient increases in salivary flow, neither drug addresses the underlying disease process or leads to increases in basal nonstimulated salivary flow.[27] Systemic and biologic agents are being

investigated for use in Sjögren syndrome. A study on interferon alfa, an immunomodulator, showed an improvement in subjective oral and ocular dryness and an increase in nonstimulated whole saliva flow.[7] A smaller study showed improvement in histologically normal-appearing minor salivary gland lip biopsies in patients treated with oral interferon alfa.[27] Trials of tumor necrosis factor antagonists have shown varied results. The largest trial of these agents showed no improvement in oral dryness, ocular dryness, or objective tests, including the Schirmer test and focus score on labial salivary gland biopsy.[8] In this study, 103 patients were randomized to infliximab (Remicade) infusions or placebo and evaluated at 10 and 22 weeks.

SYSTEMIC SYMPTOMS

Antimalarial medications and corticosteroids are being re-evaluated in the treatment of Sjögren syndrome.[28] 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.[28]

Prognosis

The most serious complication associated with primary Sjögren syndrome is the development of a lymphoproliferative disease, primarily non-Hodgkin lymphoma. Multiple studies have shown an increase in the risk of lymphoproliferative disease, but no increase in all-cause mortality.[29-31] In contrast with primary Sjögren syndrome, other rheumatologic diseases, including lupus, rheumatoid arthritis, and scleroderma, have been associated with increased mortality rates.[29] The risk of lymphoma in patients with primary Sjögren syndrome is 40 times that of the general population.[1] A prospective study of 484 Swedish patients showed that lymphoproliferative diseases caused six of 34 deaths (18 percent) in the seven years of follow-up, with an average age of 75 years at the time of death.[29] However, this study did not show an increase in rates of all-cause mortality in persons with primary Sjögren syndrome compared with the general population.[29] A larger cohort study of 723 Greek patients with 4,384 person-years of follow-up found that seven of 39 deaths (18 percent) were caused by lymphoma.[31] A total of 30 cases of lymphoma were recorded, with an average follow-up of six years.

Multiple studies have shown that low levels of complement protein C3 or C4 at the time of diagnosis are associated with a higher rate of lymphoproliferative disease and a higher mortality rate.[29,31-34] In addition to hypocomplementemia, vasculitis and severe involvement in parotid scintigraphy have been linked to lower survival rates.[34]

Although there is no definitive evidence to support screening guidelines for lymphoproliferative diseases in patients with Sjögren syndrome, the following features should raise the physician's index of suspicion: enlarged parotid glands, regional or general lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, vasculitis, and hypergammaglobulinemia.[1]

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REFERENCES

1. Fox RI. Sjögren's syndrome. *Lancet*. 2005;366 (9482):321-331.
2. Sánchez-Guerrero J, Pérez-Dosal MR, Cárdenas-Velázquez F, et al. Prevalence of Sjögren's syndrome in ambulatory patients according to the American-European Consensus Group criteria. *Rheumatology (Oxford)*. 2005;44(2):235-240.
3. Pillemer SR, Matteson EL, Jacobsson LT, et al. Incidence of physician-diagnosed primary Sjögren syndrome in residents of Olmsted County, Minnesota. *Mayo Clin Proc*. 2001;76(6):593-599.
4. García-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjögren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine (Baltimore)*. 2002;81(4):270-280.
5. Hansen A, Lipsky PE, Dörner T. Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. *Curr Opin Rheumatol*. 2005;17(5):558-565.
6. Tzioufas AG, Wassmuth R, Dafni UG, et al. Clinical, immunological, and immunogenetic aspects of autoantibody production against Ro/SSA, La/SSB and their linear epitopes in primary Sjögren's syndrome (pSS): a European multicentre study. *Ann Rheum Dis*. 2002;61(5):398-404.
7. Cummins MJ, Papas A, Kammer GM, Fox PC. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. *Arthritis Rheum*. 2003;49(4):585-593.
8. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004;50(4):1270-1276.
9. Vivino FB, Katz WA. Sjogren's syndrome: clinical picture and diagnostic tests. *J Musc Med*. 1995;12(3):40-52.
10. al-Hashimi I. The management of Sjögren's syndrome in dental practice. *J Am Dent Assoc*. 2001; 132(10):1409-1417.
11. Ovchinsky A, Har-El G. Salivary gland enlargement. In: Lucent FE, ed. *Essentials of Otolaryngology*. 5th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins;2003:223-226.
12. Al-Hashimi I, Khuder S, Haghighat N, Zipp M. Frequency and predictive value of the clinical manifestations in Sjögren's syndrome. *J Oral Pathol Med*. 2001;30(1):1-6.
13. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren's syndrome. *Arch Intern Med*. 2004;164(12):1275-1284.
14. Pertovaara M, Korpela M, Uusitalo H, et al. Clinical follow up study of 87 patients with sicca symptoms (dryness of eyes or mouth, or both). *Ann Rheum Dis*. 1999;58(7):423-427.
15. Vitali C, Bombadieri S, Jonsson S, et al., for the European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002;61(6):554-558.
16. Fox RI, Stern M, Michelson P. Update in Sjögren syndrome. *Curr Opin Rheumatol*. 2000;12(5):391-398.
17. Carter SR. Eyelid disorders: diagnosis and management. *Am Fam Physician*. 1998;57(11):2695-2702.
18. Sreebny LM, Yu A, Green A, Valdini A. Xerostomia in diabetes mellitus. *Diabetes Care*. 1992;15(7):900-904.
19. Kim J. The use of vital dyes in corneal disease. *Curr Opin Ophthalmol*. 2000;11(4):241-247.
20. Whitcher JP. The treatment of dry eyes. *Br J Ophthalmol*. 2004;88(5):603-604.
21. Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis*. 2003;62(12):1204-1207.
22. Ono M, Takamura E, Shinozaki K, et al. Therapeutic effect of cevimeline on dry eye in patients with Sjögren's syndrome: a randomized, double-blind clinical study. *Am J Ophthalmol*. 2004;138(1):6-17.
23. Ship JA. Diagnosing, managing, and preventing salivary gland disorders. *Oral Dis*. 2002;8(2):77-89.
24. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control [published correction appears in *J Am Dent Assoc*. 2006;137(4):447]. *J Am Dent Assoc*. 2006;137(2):190-196.
25. Wu CH, Hsieh SC, Lee KL, Li KJ, Lu MC, Yu CL. Pilocarpine hydrochloride for the treatment of xerostomia in patients with Sjögren's syndrome in Taiwan—a double-blind, placebo-controlled trial. *J Formos Med Assoc*. 2006;105(10):796-803.
26. Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patient's with Sjögren syndrome: a randomized trial. *Arch Intern Med*. 2002; 162(11):1293-1300.
27. Shiozawa S, Tanaka Y, Shiozawa K. Single-blinded controlled trial of low-dose oral IFN-alpha for the treatment of xerostomia in patients with Sjögren's syndrome. *J Interferon Cytokine Res*. 1998;18(4):255-262.
28. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. *Ann Rheum Dis*. 2005;64(3):347-354.
29. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. *Arthritis Rheum*. 2004;50(4):1262-1269.
30. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005; 165(20):2337-2344.
31. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. *Arthritis Rheum*. 2002;46(3):741-747.
32. Ramos-Casals M, Brito-Zerón P, Yagüe J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. *Rheumatology (Oxford)*. 2005;44(1):89-94.
33. Skopouli FN, Dafni U, Ioannidis JP, Moutsopouls HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. *Semin Arthritis Rheum*. 2000;29(5):296-304.
34. Brito-Zerón P, Ramos-Casals M, Bove A, Sentis J, Font J. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. *Rheumatology (Oxford)*. 2007;46(8):1359-1362.