

# Update on Sjögren Syndrome and Other Causes of Sicca in Older Adults



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## KEYWORDS

• Sjögren syndrome • Dry eye • Aging • Salivary hypofunction • Xerostomia

## KEY POINTS

- Dryness of the eyes, mouth, and other mucosal membranes (sicca) is reported by up to 30% of persons over the age of 65.
- Sjögren syndrome is the prototypical autoimmune illness that causes dry eyes and dry mouth and is an important consideration in individuals presenting with these symptoms.
- Diagnosis requires the presence of anti-SSA and/or anti-SSB antibodies, or a minor salivary gland biopsy showing at least 1 tightly aggregated periductal lymphocytic aggregate per 4 mm<sup>2</sup> of glandular tissue section.
- Management requires attention to both the glandular (ocular and oral dryness, glandular enlargement) and extraglandular manifestations (eg, arthritis, pneumonitis, nephritis, vasculitis).

## INTRODUCTION

Henrik Sjögren used the term “sicca syndrome” to describe the disease that he studied extensively during his lifetime, beginning with a comprehensive analysis of 19 patients that he completed in 1933 as an ophthalmologist in training.<sup>1,2</sup> The characteristic phenotypic features included severe ocular and oral mucosal dryness

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afflicting most often postmenopausal women, many of whom had associated rheumatoid arthritis. Sicca syndrome and Sjögren syndrome became synonymous. However, we now know that most older adults with sicca syndrome (ie, oral and ocular mucosal dryness) do not have Sjögren syndrome. As currently defined, Sjögren syndrome is a systemic rheumatic disease with autoimmune-induced inflammation of the lacrimal and salivary glands, resulting in impaired tear and saliva production. The distinction between these 2 entities is important, because the identification of those patients with an autoimmune basis for their sicca manifestations is the first step in deciding whether therapies directed at the immune system might be beneficial and avoiding such therapies and their attendant risks in patients with nonautoimmune sicca syndrome.

This article reviews the clinical manifestations, differential diagnosis, and medical evaluation of older adults with dry eyes and mouth, as well as the approach to the diagnosis and management of Sjögren syndrome.

## EPIDEMIOLOGY OF SICCA

Symptoms of dryness of the eyes, mouth, and vagina (in women) increase with age and reach up to 30% in persons more than the age of 65 years, particularly in women.<sup>3-9</sup> Objective evidence of diminished tear or saliva production is much less frequent,<sup>6,7,10</sup> indicating the weak association between dryness symptoms and objective measures. Both dry eye and dry mouth symptoms were reported by 4.4% of an elderly population, age 65 to 84 years, in Salisbury, Maryland,<sup>11</sup> and had no association with markers of systemic autoimmunity. The prevalence of Sjögren syndrome in this population was only 0.04%.<sup>12</sup>

## DRY EYE

Dry eye manifests most often with ocular irritation, including burning, stinging, soreness, and a foreign body sensation. The symptoms are aggravated by exposure to low humidity, wind, or air drafts, as well as prolonged visual attention, including reading. Less frequent symptoms include blurred vision, excess tearing, and blepharospasm.

Dry eye is generally caused by diminished tear production or by excessive tear evaporation<sup>13</sup> (**Box 1**). The former is most often caused by lacrimal gland disease,

<b>Box 1</b>	
<b>Common causes of dry eye</b>	
<b>Aqueous Tear Deficiency</b>	<b>Evaporative Tear Deficiency</b>
<ul style="list-style-type: none"> <li>• SS</li> <li>• Age-related dry eye</li> <li>• Systemic medications (eg, antihistamines, <math>\beta</math>-blockers, antispasmodics, diuretics)</li> <li>• Lacrimal gland duct obstruction (eg, cicatricial pemphigoid, mucous membrane pemphigoid, trachoma, erythema multiforme, burns)</li> <li>• Ocular sensory loss leading to reflex hyposecretion (eg, diabetes mellitus, corneal surgery, contact lens wear, trigeminal nerve injury)</li> <li>• Lacrimal gland infiltration (eg, sarcoid, lymphoma, graft vs host disease, AIDS, IgG4-related disease)</li> </ul>	<ul style="list-style-type: none"> <li>• Meibomian gland dysfunction (posterior blepharitis)</li> <li>• Exophthalmos, poor lid apposition, lid deformity</li> <li>• Low blink rate</li> <li>• Ocular surface disorders (eg, vitamin A deficiency, toxicity from topical drugs/preservatives, contact lens wear)</li> <li>• Ocular surface disease (eg, allergic conjunctivitis)</li> </ul>
<p><i>Abbreviations:</i> Ig, immunoglobulin; SS, Sjögren syndrome.</p>	

but can result from lacrimal gland duct obstruction or reflex hyposecretion related to corneal sensory loss. Excessive evaporation from Meibomian gland dysfunction and other forms of blepharitis is more common. Other causes of dryness include incomplete lid closure during sleep, allergic conjunctivitis, and trachoma.

The assessment of dry eye requires multiple tests (**Box 2**). The Schirmer test measures tear production<sup>14</sup> and can be performed reliably by a rheumatologist in a clinic setting. A sterile rectangular strip of filter paper, rounded and notched at the proximal end, is folded over the lower eyelid at the midpoint between the middle and lateral fornix of each eye. The patient is then asked to close the eyes gently during the 5-minute duration of the test. The extent of tear wicking or wetting is recorded in millimeters. The Schirmer test can be performed with or without anesthesia to measure basal and reflex tear secretion, respectively. Without anesthesia, a Schirmer test result of less than 5 mm in at least 1 eye is abnormal. This test is imperfect in the elderly, because the degree of wetting decreases with age. In 2 population-based surveys of elderly individuals ( $\geq 65$  years), the prevalence of an abnormal Schirmer test ranged from 12% to 58%.<sup>4,6</sup>

Ocular surface staining with vital dyes allows slit lamp visualization of devitalized conjunctival cells and corneal epithelial defects. It is more sensitive than the Schirmer test for detecting dry eye. Lissamine green is most commonly used to stain the conjunctiva and fluorescein the cornea. The extent of ocular surface staining is a measure of dryness-induced ocular surface damage, is one of the classification criteria for Sjögren syndrome, and can be scored using methods described by van Bijsterveld<sup>15</sup> and by the Sjögren International Collaborative Clinical Alliance.<sup>16,17</sup>

The tear breakup time test is used to assess the stability of the tear film<sup>18</sup> and is typically abnormal in Meibomian gland dysfunction. Tear osmolarity measurement<sup>19,20</sup> is the best for predicting dry eye severity.<sup>20</sup>

## XEROSTOMIA AND SALIVARY HYPOFUNCTION

Symptoms of dry mouth, termed xerostomia, include burning, dry lips, alteration of taste, and a sense of having an inadequate amount of saliva. There also may be difficulty speaking, swallowing, and wearing dentures. The need to sip water to swallow dry food is an important marker of reduced salivary function.<sup>21</sup> Halitosis, painful tongue fissures, mucosal ulcers, and pain with ingestion of spicy or acidic foods

### Box 2

#### Tests used to assess dry eye disease

Test	Abnormal Value	Significance of Abnormal Test
Schirmer	<5 mm/5 min in either eye	Inadequate tear production
Ocular surface staining	Score $\geq 4$ (von Bijsterveld) <sup>15</sup> Score $\geq 3$ (SICCA) <sup>17</sup>	Damage to the ocular surface
Tear breakup time	<10 s	Poor tear film stability, as seen in Meibomian gland dysfunction
Tear osmolarity	$\geq 308$ mOsm/L in either eye	Excessive tear evaporation, lacrimal gland disease, or ocular surface inflammation

*Abbreviation:* SICCA, Sjögren's International Collaborative Clinical Alliance.

*Data from* van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol* 1969;82(1):10–4; and Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's syndrome International Registry. *Am J Ophthalmol* 2010;149(3):405–15.

may stem from candidal overgrowth on the oral mucosa. The relation between salivation and xerostomia is complex. Dawes<sup>22</sup> showed that healthy patients report dry mouth symptoms when their baseline salivary flow is reduced by 50%, even if the residual salivary flow level remains within the broad range of normal.

Saliva is produced by the major (parotid, submandibular, sublingual) and myriad submucosal minor salivary glands. The parotid glands only produce saliva on gustatory or olfactory stimulation. Saliva is continually secreted by the sublingual, submandibular, and minor salivary glands. This basal secretion is crucial for maintaining oral health.

Both unstimulated and stimulated salivary flow rates are measured. Saliva that pools in the mouth without stimulation can be collected for 5 to 15 minutes, providing a measure of so-called whole saliva production in a clinic setting (**Box 3**). It is considered the most relevant measure of oral health. Stimulated whole salivary flow rates can be measured with the patient chewing gum, preweighed gauze, or paraffin (eg, Parafilm) and are not generally affected by medication use. With special research techniques, stimulated (eg, with lemon juice on the tongue) and unstimulated saliva flow rates can be measured from the individual parotid glands or sublingual/submandibular glands.

Human salivary glands undergo atrophy with age (**Fig. 1**). In morphometric studies, aging was associated with acinar loss and replacement with fat and connective tissue.<sup>23,24</sup> Whole unstimulated saliva flow rates decrease with age, which may contribute to the age-dependent increase in dental caries.<sup>25</sup> However, this is not true for stimulated parotid saliva flow rates.<sup>26</sup>

There are multiple potential causes for xerostomia and salivary hypofunction (**Box 4**).<sup>10</sup> Side effects from medications commonly used in older individuals are the most common.

### VAGINAL DRYNESS

Vaginal dryness, dyspareunia, and vulvar pruritus are common symptoms among postmenopausal women. These symptoms relate to menopause-related decreases in the levels of estrogen and other sex steroids, but can also have other causes.

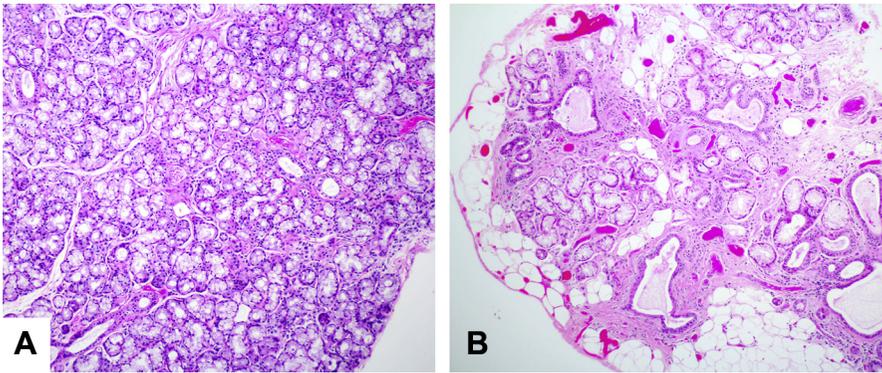
#### Box 3

##### Measurement of unstimulated whole salivary flow rate

Unstimulated whole saliva collection measures saliva production under resting or basal conditions. The patient should not have had anything to eat or drink for 90 minutes before the procedure. The use of a parasympathomimetic should be discontinued for 12 hours before the procedure, and the use of artificial saliva should be stopped 3 hours before. During the collection procedure, the patient is instructed to minimize actions that can stimulate saliva (talking, increased orofacial movement) and should not swallow. At time 0, any saliva present in the mouth is cleared by swallowing. For the subsequent 5 minutes, any saliva collected in the mouth is emptied into a preweighed tube every minute (ie, 5 times). This collecting tube then is weighed to determine a postcollection weight. The difference between the precollection and postcollection weight is determined, and this represents the unstimulated whole saliva production for 5 minutes. To convert to a volume of saliva from the weight of saliva, an assumption is made that saliva is similar to water, with 1 g of water/saliva at 4°C equaling 1 mL of saliva/water.

Less than 0.100 mL/min is considered a reduced unstimulated salivary flow rate.

*From Wu AJ. Optimizing dry mouth treatment for individuals with Sjögren's syndrome. Rheum Dis Clin North Am 2008;34(4):1004; with permission.*



**Fig. 1.** Histopathology of minor labial salivary glands. The sections are from biopsies of a 28-year-old woman (A) and a 65-year-old woman (B), shown at the same magnification. Neither had Sjögren syndrome. (A) This histopathologic section shows normal tissue, with confluent mucous acini and normal-sized intralobular ducts. (B) In contrast, this section shows extensive acinar loss, interstitial fibrosis, ductal dilatation, and fatty replacement. These changes are often seen to varying degrees in older patients (stain: hematoxylin and eosin; original magnification  $\times 100$ ).

In 2014, 2 international societies recommended that the range of symptoms and signs associated with menopause be termed the genitourinary syndrome of menopause.<sup>27</sup> These symptoms include genital dryness, burning, irritation, inadequate lubrication, dyspareunia, urinary urgency, dysuria, and recurrent urinary tract infections. Similar symptoms are also seen with infectious vaginitis, irritant or allergic vulvitis or vaginitis, vulvovaginal dermatoses, hypertonic pelvic floor muscle dysfunction, painful bladder syndrome/interstitial cystitis, vulvodynia, and pudendal neuralgia.<sup>27</sup>

In women affected by Sjögren syndrome, vaginal dryness can be severe and affect sexual ability and pleasure.<sup>28</sup> There is scant information regarding the cause of this dryness. One hypothesis is that the Skene and related glands of the vaginal introitus are affected in the same manner as exocrine glands found elsewhere.<sup>29</sup> There has been no histopathologic confirmation of this theory to date. Biopsies of vaginal mucosa from patients with Sjögren syndrome show subepithelial inflammatory infiltrates more frequently than those from controls.<sup>30</sup> A negative effect of this infiltrate on the transudation of serous fluid into the vaginal vault constitutes an alternative hypothesis for vaginal dryness in women with Sjögren syndrome.

#### Box 4

##### Common causes of dry mouth

- Medications, including antidepressants, anticholinergics, antispasmodics, antihypertensives, antihistamines, sedatives, and diuretics
- Sjögren syndrome
- Diabetes mellitus
- Head and neck irradiation
- Dehydration
- Parkinson disease

## SJÖGREN SYNDROME

Sjögren syndrome is the prototypical illness of dryness of the eyes and mouth. It is a chronic systemic autoimmune disease characterized by dry eyes and dry mouth, arising from autoimmune-induced inflammation of the lacrimal and salivary glands. This chronic inflammatory process gradually leads to glandular injury and related dysfunction over the course of years, eventually causing the cardinal symptoms of dry eyes and mouth. It primarily affects perimenopausal and postmenopausal women and can occur in a primary form or in association with another systemic autoimmune disease (termed secondary Sjögren syndrome). The reported prevalence of primary Sjögren syndrome in population-based studies ranges from 0.01% to 0.09%.<sup>31</sup> Sjögren syndrome is present in up to 17% of patients with rheumatoid arthritis.<sup>32,33</sup> Because the latter is a disease whose prevalence reaches 1.1% in the United States,<sup>34</sup> this renders Sjögren syndrome the second most common systemic rheumatic disease. Key features are shown in **Box 5**.

Sjögren syndrome disease onset is uncommon after the age of 65 or 70 years.<sup>35,36</sup> Older patients with Sjögren syndrome, compared with younger ones, have a lower frequency of serologic abnormalities, such as anti-SSA, anti-SSB, rheumatoid factor, and hyperglobulinemia.<sup>37</sup> Parotid enlargement, arthralgia, and Raynaud phenomenon are also less common, although higher frequencies of lung involvement and anemia have been noted.<sup>36</sup> A distinct subset of older patients with Sjögren syndrome with anticentromere antibodies is characterized by the Raynaud phenomenon, overlap features of limited systemic sclerosis, and more severe salivary and lacrimal gland dysfunction.<sup>38</sup>

The clinical presentation of Sjögren syndrome is varied, but is most often that of mucosal dryness (**Box 6**).

Sjögren syndrome is associated with a variety of systemic manifestations (**Box 7**). Some are direct manifestations of the disease, whereas others represent coincidental autoimmune diseases. Apart from symptoms of fatigue, joint pain, and mild cognitive impairment (often termed brain fog), the prevalence of these organ-specific manifestations is each less than 20%.<sup>39</sup>

### Box 5

#### Key clinical features of Sjögren syndrome

- Predominant involvement of women, with female to male ratios of more than 10:1.
- Diagnosis most commonly established in the fifth and sixth decades of life, although symptoms of dryness may precede the diagnosis by many years.
- Affects individuals across the age spectrum, including children, but most commonly women in the perimenopausal years of life.
- Extraglandular manifestations in approximately 50% of patients, including constitutional symptoms (eg, fatigue and mild cognitive impairment) and other systemic manifestations, with involvement of diverse organ systems.
- Presence of anti-SSA/Ro and anti-SSB/La in 60% to 80% of patients.<sup>71–74</sup>
- Increased risk of B-cell non-Hodgkin lymphoma, particularly MALT and diffuse B-cell lymphoma. The relative risk of non-Hodgkin lymphoma ranges from 4.8 for primary to 9.6 for secondary SS,<sup>75</sup> with an estimated lifetime risk of 5% to 10%.<sup>76</sup>

*Abbreviation:* MALT, mucosa-associated lymphoid tissue.

*Data from Refs.*<sup>71–76</sup>

**Box 6****Modes of presentation of Sjögren syndrome**

- Symptoms or signs of dry eyes and mouth
- Episodic or persistent salivary gland enlargement
- Sudden increase in dental caries
- An established connective tissue disease complicated by dry eyes or mouth
- Extraglandular disease (eg, annular erythema, cryoglobulinemia, peripheral neuropathy, or interstitial pneumonitis)
- Abnormal serologic test, such as anti-SSA and/or anti-SSB antibodies
- MALT lymphoma of a salivary gland

*Abbreviation:* MALT, mucosa-associated lymphoid tissue.

The natural history is generally one of stability, with a slow decline in lacrimal and salivary gland function. Patients may report periods of worsening sicca or fatigue and uncommonly have the types of systemic disease flares seen in systemic lupus or rheumatoid arthritis. There is no increase in overall mortality according to a recent metaanalysis, but patients with specific extraglandular manifestations, including those with vasculitis, cryoglobulinemia, pulmonary disease, and lymphoma, have been identified as having higher mortality.<sup>40,41</sup>

**Box 7****Systemic manifestations of Sjögren syndrome**

<b>Organ Involvement</b>	<b>Manifestation</b>
Constitutional	Fatigue Mild cognitive disturbance
Musculoskeletal	Arthritis/arthralgia Myositis (especially inclusion body myositis)
Cutaneous	Annular erythema Xerosis Palpable purpura
Pulmonary	Interstitial pneumonitis Follicular bronchiolitis
Vascular	Raynaud's phenomenon Vasculitis
Gastrointestinal	Atrophic gastritis Primary biliary cirrhosis
Endocrine	Autoimmune thyroid disease
Cardiac	Pericarditis
Renal	Interstitial nephritis with renal tubular acidosis Membranoproliferative glomerulonephritis
Hematologic	Leukopenia, neutropenia Thrombocytopenia Anemia Monoclonal gammopathy
Lymphoproliferative	Cryoglobulinemia Lymphoma
Neurologic	Peripheral neuropathy Ataxic ganglionopathy Myelitis (including neuromyelitis optica)

## DIAGNOSIS OF SJÖGREN SYNDROME

The diagnosis requires evidence of autoimmune-induced inflammation targeting the salivary or lacrimal glands. In 2016, a new set of classification criteria was jointly endorsed by the American College of Rheumatology and the European League against Rheumatism (Box 8).<sup>42</sup> These criteria have supplanted 2 previous sets, those of the American-European Consensus Group (2002) and the American College of Rheumatology (2012).<sup>43,44</sup> The new criteria incorporate elements of these previous sets and eliminate some that were outdated, but maintain the requirement that the

### Box 8

#### ACR-EULAR classification criteria for primary SS

Item	Weight/Score
The classification of primary SS applies to any individual who meets the inclusion criteria, <sup>a</sup> does not have any of the conditions listed as exclusion criteria, <sup>b</sup> and has a score of $\geq 4$ when the weights from the 5 criteria items below are summed:	
Labial salivary gland with focal lymphocytic sialadenitis and focus score of $\geq 1$ foci/4 mm <sup>b,c</sup>	3
Anti-Ro/SSA positive	3
Ocular Staining Score of $\geq 5$ (or van Bijsterveld score of $\geq 4$ ) in $\geq 1$ eye <sup>d,e</sup>	1
Schirmer's test of $\leq 5$ mm/5 min in $\geq 1$ eye <sup>d</sup>	1
Unstimulated whole saliva flow rate of $\leq 0.1$ mL/min <sup>d,f</sup>	1

**Abbreviations:** ACR-EULAR, American College of Rheumatology-European League against Rheumatism; SS, Sjögren syndrome.

<sup>a</sup> Inclusion criteria: these criteria are applicable to any patient with at least 1 symptom of ocular or oral dryness, defined as a positive response to at least 1 of the following questions: (1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (2) Do you have a recurrent sensation of sand or gravel in the eyes? (3) Do you use tear substitutes more than 3 times a day? (4) Have you had a daily feeling of dry mouth for more than 3 months? (5) Do you frequently drink liquids to aid in swallowing dry food?; or in whom there is suspicion of SS from the European League Against Rheumatism SS Disease Activity Index questionnaire (at least 1 domain with a positive item).

<sup>b</sup> Prior diagnosis of any of the following conditions would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: History of head and neck radiation treatment; active hepatitis C infection (with positive polymerase chain reaction); AIDS; sarcoidosis; amyloidosis; graft-versus-host disease; immunoglobulin G4-related disease.

<sup>c</sup> Labial salivary gland with focal lymphocytic sialadenitis and a focus score of  $\geq 1$  foci/4 mm<sup>2</sup>. The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis, and a focus score count following a protocol described in Daniels TE, Cox D, Shiboski CH, et al. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. *Arthritis Rheum* 2011;63:2021–30.

<sup>d</sup> Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications for these components to be a valid measure of oral and ocular dryness.

<sup>e</sup> Ocular staining score described by Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol* 2010;149(3):405–15. VB: van Bijsterveld score described in Van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. *Arch Ophthalmol* 1969;82:10–4.

<sup>f</sup> UWS: unstimulated whole saliva described in Navazesh M, Kumar SK, University of Southern California School of Dentistry. Measuring salivary flow: challenges and opportunities. *J Am Dent Assoc* 2008;139 Suppl:35S–40S.

From Shiboski CH, Shiboski SC, Seror R, et al. 2015 Classification criteria for Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheum* 2017;69:35–45.

diagnosis of Sjögren syndrome be only tenable if a patient has either anti-SSA antibodies or a “positive” minor salivary gland biopsy (focal lymphocytic sialadenitis with a focus score greater than or equal to 1).

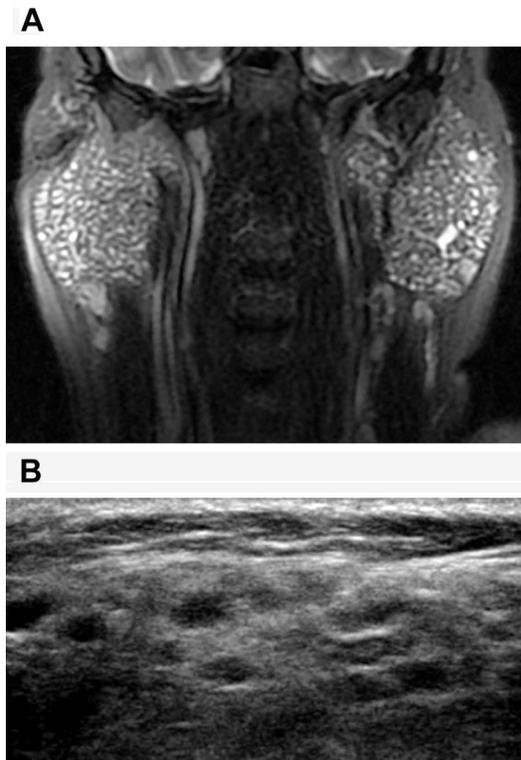
These criteria are only applicable to an individual with findings concerning for Sjögren syndrome, defined as at least 1 symptom of ocular or oral dryness (positive response to  $\geq 1$  of 5 standardized questions), salivary gland enlargement, or a characteristic extraglandular manifestation of Sjögren syndrome (as defined by a positive domain in the European League against Rheumatism Sjögren Syndrome Disease Activity Index).<sup>45</sup>

The authors use these current classification criteria as a general guide, and establish the diagnosis if a patient has an objective measure of ocular and/or oral dryness or characteristic imaging abnormalities (eg, by ultrasound imaging, MRI, or computed tomography scanning), coupled with anti-SSA antibodies or a positive lip biopsy.

The authors recommend that patients suspected of having Sjögren syndrome be evaluated as follows.

- History, seeking a history of persistent symptoms of dry eyes and/or mouth. Validated screening questions are included in the American College of Rheumatology-European League against Rheumatism Classification Criteria (see **Box 8**, footnote).
- Examination, seeking signs of salivary hypofunction and of a systemic rheumatic disease
  1. Oral examination
    - a. Is there enlargement of the lacrimal or major salivary glands? What is the texture of the major salivary glands? Are there discrete nodules or masses?
    - b. Does saliva pool under the elevated tongue when observed over the course of 1 minute?
    - c. Does the tongue have deep fissures, a hyperlobulated appearance, or absence of filiform papillae on its surface?
    - d. The Challacombe scale, available online, can be used to identify and rate the severity of oral dryness, based on physical examination findings (<http://www.challacombescale.co.uk/Challacombe-Scale-ENG.pdf>, accessed February 11, 2018).<sup>46</sup>
  2. General examination
    - a. Look for sclerodactyly, palpable purpura, synovitis, basilar pulmonary rales.
- Laboratory testing
  1. Screen for antinuclear antibody (tested by immunofluorescence assay), anti-SSA (Ro), and anti-SSB (La), and rheumatoid factor. Anti-SSA and anti-SSB antibodies can be present despite a negative antinuclear antibody test.
  2. A complete blood count, urinalysis, and chemistry profile may reveal abnormalities supportive of Sjögren syndrome, including leukopenia and neutropenia, hyperglobulinemia, renal impairment, and proteinuria.
- Ophthalmologic examination
  1. Schirmer testing is an appropriate initial test. A formal ophthalmologic examination serves not only to confirm the diagnosis of dry eye but also to define the contributing causes, such as Meibomian gland dysfunction and conjunctivochalasis. Guidelines for this evaluation can be found at <https://sicca-online.ucsf.edu/documents/eye-exam-SOP.pdf>.
- Sialometry
  1. Documentation of salivary hypofunction is only necessary if the eye examination does not show dry eye disease (see **Box 3**).

- Labial gland biopsy
  1. A labial gland biopsy, best performed by an oral surgeon, is required for diagnosis if the patient lacks anti-SSA and/or anti-SSB antibodies. The biopsy also has value in excluding alternative diagnoses (eg, sarcoid, amyloid, mucosa-associated lymphoid tissue lymphoma, and immunoglobulin [Ig] G4-related disease). Guidelines for its performance can be found at <https://sicca-online.ucsf.edu/documents/Oral-Saliva-SOP.pdf>.
- Imaging (**Fig. 2**)
  1. Salivary gland ultrasound imaging is favored because of its low cost and lack of ionizing radiation. The presence of multiple ovoid hypoechoic lesions, often bounded by hyperechoic bands, correlates with markers of more severe disease. These imaging abnormalities have high specificity for the diagnosis, but only moderate sensitivity.<sup>47–51</sup>
  2. Computed tomography scanning is not recommended because of the radiation exposure. However, the presence of multiple punctate calcifications within the parotid glands has high specificity.<sup>52</sup>
  3. MRI of the parotid glands may reveal heterogeneity of signal intensity on both T1-weighted and T2-weighted images, with both hypointense and hyperintense foci measuring 1 to 4 mm in diameter.<sup>53</sup>



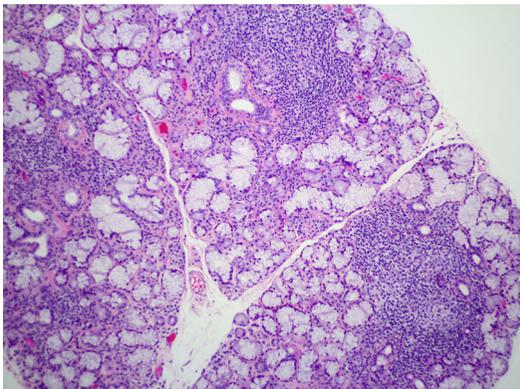
**Fig. 2.** Imaging techniques in Sjögren syndrome. This patient has bilateral symmetric parotid gland enlargement, seen best on the T2 fat-suppressed MRI (A). Note the multiple T2-hyperintense foci scattered throughout both glands, a characteristic finding. With ultrasound imaging (B), multiple hypoechoic rounded lesions with convex borders are noted throughout the glandular parenchyma. In normal parotid gland tissue, the parenchyma has a homogeneous appearance with ultrasound imaging.

Be aware of common pitfalls in the diagnostic evaluation. These include the following.

- a. Assessment of sicca manifestations. Certain historical features distinguish the sicca manifestations of Sjögren syndrome from symptoms often experienced by otherwise healthy people. The symptoms of ocular and oral dryness should be a daily, persistent problem and have been present for at least 3 months. The ocular dryness should be severe enough to mandate the use of tear supplements at least 3 times per day. Positive responses to the following 2 questions are highly predictive of salivary hypofunction<sup>21</sup>: Do you sip liquids to aid in swallowing dry foods? Does your mouth feel dry when eating a meal? The ophthalmologist's assessment of a dry eye patient for Sjögren syndrome should include a Schirmer test and conjunctival staining with Lissamine green (as opposed to simply assessing corneal staining with fluorescein), because positive results of these 2 tests correlate best with positive serology and positive lip biopsy.<sup>54</sup>
- b. Antibody testing. Antibodies to SSA and SSB are not specific. They are found in systemic lupus and inflammatory myopathies, and are seen in up to 0.9% of healthy women in the US population.<sup>55</sup> With modern multiplex assay technology, weakly positive test results for anti-SSA and anti-SSB must also be interpreted with caution, because they have a less robust association with Sjögren syndrome. In particular, the finding of anti-SSB antibodies alone, in the absence of anti-SSA antibodies, does not support a diagnosis of Sjögren syndrome<sup>56</sup> and has, thus, been eliminated as a classification criterion for the disease.<sup>42</sup> The authors recommend the performance of a labial gland biopsy in the diagnostic evaluation of patients with weakly positive anti-SSA or anti-SSB antibodies (or anti-SSB alone), in whom Sjögren syndrome is suspected.

A commercial assay for 3 murine tissue-specific autoantibodies, carbonic anhydrase 6, parotid-specific protein, and salivary protein-1, is now available as a test for early Sjögren syndrome. However, the ability of these antibodies to mark individuals who are destined to develop Sjögren syndrome has not been validated.<sup>57</sup>

- c. Labial gland biopsy performance and interpretation. The histopathology of the minor salivary gland, termed focal lymphocytic sialadenitis, is characterized by lymphocytic aggregates that surround intralobular salivary ducts (Fig. 3) and

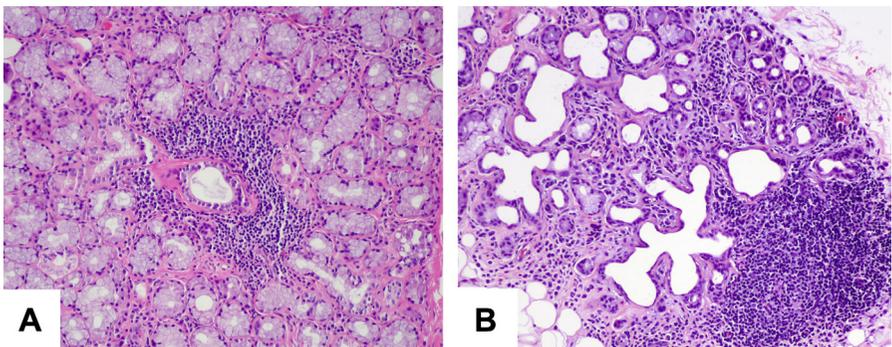


**Fig. 3.** Focal lymphocytic sialadenitis. This section of a labial salivary gland biopsy shows the typical features of focal lymphocytic sialadenitis. Note the tightly aggregated lymphocytes surrounding ducts and adjacent to normal-appearing mucous acini. At least 3 foci are evident (stain: hematoxylin and eosin; original magnification  $\times 100$ ).

are adjacent to normal-appearing mucus-secreting acini. The number of these lymphocytic aggregates per 4 mm<sup>2</sup> of glandular tissue section equates to the focus score. A score greater than or equal to 1 is a criterion for the classification of Sjögren syndrome and has been validated as the best cutoff value differentiating Sjögren syndrome from non-Sjögren syndrome controls.<sup>58</sup> Accurate assessment of the focus score requires adequate glandular tissue for analysis; ideally, 3-5 glands should be collected at the time of biopsy and the total surface area of the glandular surface area should be at least 4 mm<sup>2</sup> (preferably 10–20 mm<sup>2</sup> because the focus score can be overestimated in smaller specimens).<sup>58</sup> The total glandular surface area of the tissue section should be measured with a calibrated reticule in the microscope eyepiece or with digital image software. Because chronic inflammation of the salivary gland can also arise from ductal obstruction and other forms of glandular injury, care must be taken to exclude from the focus score lymphocytic aggregates in areas of severe acinar loss, ductal dilatation, and fibrosis (**Fig. 4**). Assessment of the labial gland biopsy for Sjögren syndrome may require that the slides be forwarded to a reference laboratory for interpretation and proper calculation of the focus score.

The differential diagnosis of Sjögren syndrome primarily includes alternative causes of sicca symptoms, salivary and/or lacrimal gland enlargement, and the characteristic serologic abnormalities.

- Sicca complex in the elderly: age-related interstitial fibrosis, acinar atrophy, and nonspecific chronic inflammation in the labial gland biopsy may be misinterpreted as indicating Sjögren syndrome (see **Fig. 4**).
- Salivary and/or lacrimal gland enlargement: Particular attention should be paid to the possibility of lymphoma. IgG-4 related disease is most common in older men. It may present as unilateral submandibular gland enlargement (Küttner tumor) or parotid and lacrimal gland enlargement. Other diagnostic possibilities include amyloid infiltration, sarcoidosis, human immunodeficiency virus infection, bulimia, and hyperlipoproteinemia.<sup>59</sup>



**Fig. 4.** Potential misinterpretation of labial gland biopsies. (A) The lymphocytic focus is typical of that seen in focal lymphocytic sialadenitis, being centered on a duct and adjacent to normal-appearing mucus-secreting acini. (B) In contrast, the lymphocytic focus here is present within a gland lobule marked by interstitial fibrosis, ductal dilatation, and marked acinar loss. This focus should not be interpreted as representative of Sjögren syndrome (stain: hematoxylin and eosin; original magnification  $\times 100$ ).

- Serologic abnormalities: antinuclear antibodies, rheumatoid factor, and monoclonal proteins are more prevalent in the elderly population.<sup>55</sup> Thus, positive tests must be interpreted cautiously when they coincide with symptoms or signs of oral or ocular dryness.

## MANAGEMENT OF SJÖGREN SYNDROME

Most patients only require topical and systemic treatments directed at alleviating their ocular, oral, and vaginal dryness; preventing dental decay; and managing oral candidiasis. Patients with systemic manifestations, including those with joint pain, skin lesions, and internal organ involvement, may benefit from immunomodulatory treatments. All patients with Sjögren syndrome require monitoring for disease complications, especially lymphoma. The British Society for Rheumatology has recently established guidelines for the management of Sjögren syndrome.<sup>60</sup>

The management of ocular dryness depends on its severity and the patient's response to therapy.<sup>61</sup> Avoidance of wind and smoke, and the use of protective eyewear, can be helpful for all patients. Artificial tears with a demulcent (eg, methylcellulose, propylene glycol, and glycerin) are a mainstay of treatment. Patients should use preservative-free drops if drops are instilled 4 or more times a day. Use of thicker ocular gels and ointments before bed can help with the dryness that occurs during sleep. Supplementation of the diet with omega-3 essential fatty acids has been shown to be of benefit. The use of topical cyclosporine and steroid solutions can be useful in a variety of dry eye conditions, but should be undertaken in consultation with an ophthalmologist. Punctal plugs to preserve tears are often used in moderate to severe dry eye. Patients with more severe dry eye disease may require the use of moisture chamber spectacles, autologous serum tears, contact lenses, or scleral prostheses.

The prevention of oral dryness includes maintaining good hydration and avoiding medications that worsen dryness. Patients should be counseled to be more aware of factors that can aggravate dryness, such as low-humidity environments and mouth breathing. Frequent sips of oral solutions can be helpful, with options ranging from water to artificial saliva. Sucking on sugar-free hard candies helps to stimulate saliva flow. Oral hygiene and dental care are essential in preserving dentition in persons with pathologic oral dryness.

Muscarinic agonists, such as pilocarpine and cevimeline, can substantially increase saliva and, to a lesser extent, tear flow. However, overall tolerance of these agents may be hampered by cholinergic side effects of excessive sweating, increased urinary frequency, flushing, chills, rhinitis, nausea, and diarrhea. Care must be taken when these medications are prescribed to the elderly.

Vaginal moisturizers and lubricants, including olive and vitamin E oils, are initial treatment options for vaginal dryness. Vitamin E capsules can be opened and the oil used in and around the vagina. A suppository containing hyaluronic acid, vitamin E, and vitamin A, used once daily for 14 days, then once every other day for the next 2 weeks, can be effective.<sup>62</sup> Obtaining these suppositories requires a compounding pharmacist. Low-dose vaginal estrogen therapy is indicated if symptoms do not improve with these nonprescription measures. The available options include a vaginal cream, insert, ring, or soft gel capsule.<sup>63</sup>

Hydroxychloroquine is commonly used for the management of joint pain and/or fatigue. However, clinical trials with this drug have shown mixed results, with none showing major clinical improvements.<sup>64–66</sup> The effect of immunosuppressive therapies on the glandular manifestations has been disappointing to date. The effect of

rituximab on Sjögren syndrome dryness is still being evaluated, with potential benefit being observed in a small, double-blind, placebo-controlled trial,<sup>67</sup> but not in 2 larger ones.<sup>68,69</sup> Prolonged therapy may be required for benefit.<sup>70</sup>

## SUMMARY

Dryness of the eyes and mouth is a prevalent symptom in the population, especially among the elderly, and is most often related to the side effects of medications. However, there is a broad differential diagnosis for each symptom, and careful evaluation is important to define the cause and correct treatment. Sjögren syndrome is the prototypic disease that leads to these symptoms and primarily affects perimenopausal women. The diagnosis requires demonstration of an autoimmune disease underlying the sicca manifestations, either serologically or pathologically. Management can involve both topical and systemic therapies.

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