

Evaluation of patients with dry eye for the presence of primary or secondary Sjögren's syndrome

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Purpose: To assess the frequency of Sjögren's syndrome (SS), either primary or secondary to rheumatic disease, in a cohort of patients with aqueous-deficient dry eye and to determine the most accurate objective test for diagnosis of SS.

Methods: A total of 111 patients with dry eye were recruited from Minia University's Ophthalmology Outpatient Clinic (69 patients) and Rheumatology Outpatient Clinic (42 patients). The patients were screened for aqueous tear-deficient dry eye by abnormal test results of Schirmer test I (<10 mm) and tear-film break-up time (<10 seconds) in at least one eye. The diagnosis of SS was made according to the 2012 American College of Rheumatology criteria. A complete work up for SS was performed, including clinical examination, serological tests, ocular tests, and labial salivary-gland biopsy (LSGB).

Results: Of the 111 patients, 58 had aqueous-deficient dry eye: 23 in the ophthalmology clinic cohort (group I) and 35 in the rheumatology clinic cohort (group II). Three patients had pSS, and its frequency was 13% in group I and 5.2% among all studied patients. The ocular staining score is the most diagnostic ocular test (sensitivity 100% and specificity 90.9%). Anti-SSA/Ro antibody is the most accurate serological method (sensitivity 33.3% and specificity 100%). LSGB histopathology is the most diagnostic method for SS, with sensitivity, specificity, and positive and negative predictive values of 100%.

Conclusion: SS was detected with reasonable frequency among dry-eye patients, particularly pSS. Screening of dry eye for SS can select SS patients early in the disease course.

Keywords: dry eye, Sjögren's syndrome, rheumatic disease, ocular staining score, OSS, labial salivary-gland biopsy, LSGB

Introduction

Dry-eye syndrome (DES) is a common chronic multifactorial condition of the ocular surface characterized by failure to produce high-quality or sufficient tears to moisturize the eyes.¹ DES can substantially affect vision and quality of life, as symptoms often interfere with daily activities.² The International Dry Eye Workshop classified DES into aqueous-deficient and evaporative. Aqueous tear-deficient dry eye occurs when there is lacrimal acinar destruction or dysfunction with reduced lacrimal tear secretion and volume. In evaporative dry eye, there is excessive water loss from the exposed ocular surface with normal secretory function of lacrimal gland. Aqueous tear-deficient dry eye has two major subclasses: Sjögren's syndrome (SS) dry eye and non-SS dry eye.³

DES is one of the key clinical features and possibly an early clinical presentation of SS. SS is an autoimmune disorder involving multiple organs. The key feature of SS is lymphocyte infiltration of exocrine glands leading to dry eye and

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dry mouth, which are crucial presentations of SS.^{4,5} SS can present as either primary (pSS) or secondary (sSS). pSS is defined as the presence of aqueous-deficient dry eye in combination with dry mouth, sicca symptoms, extraglandular manifestations, autoantibodies, and positive focus score on labial salivary-gland biopsy (LSGB). sSS has features of pSS associated with autoimmune rheumatic diseases, such as rheumatoid arthritis (RA), which is the most common and systemic lupus erythematosus.⁶

SS is underdiagnosed in clinical practice because of its diverse presentation, leading to a significant delay in diagnosis.⁷ The lack of specific diagnostic tests combined with the high frequency of sicca symptoms in older adults makes the diagnosis of SS even more complicated.⁸ The importance of making the diagnosis is cardinal, because patients with SS are likely to have reduced quality of life as a result of pain, fatigue, depressed mood, and cognitive symptoms. More importantly, systemic involvement is common in pSS and associated with disease morbidity and mortality.^{8,9}

Many classification criteria have been used for the diagnosis. The American College of Rheumatology (ACR) criteria classification 2012 includes three objective measures to simplify the diagnosis and have high specificity.¹⁰ The aim of the current study was to assess the frequency of SS, either primary or secondary to rheumatic disease, in a cohort of patients with aqueous-deficient dry eye and to determine the most accurate objective test for diagnosis of SS.

Methods

Patients

A total of 111 patients with dry eye were recruited from Minia University's Ophthalmology Outpatient Clinic (69 patients) and Rheumatology Outpatient Clinic (42 patients). All patients were attending Minia University Hospital from October 2015 to May 2017. Patients were complaining of foreign-body sensation, burning, stinging, itching, dryness, soreness, heaviness of the lids, photophobia, or ocular fatigue. Other causes of dry eye, such as Stevens-Johnson syndrome, mucous-membrane pemphigoid, corneal surgery, sarcoidosis, trachoma, hepatitis C virus infection, and use of anticholinergic drugs, were excluded. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Faculty of Medicine, Minia University.

Written informed consent was obtained from patients to be included in the study.

Diagnostic approach for dry-eye patients for SS

Patients screened as having aqueous tear-deficient dry eye by abnormal test results of Schirmer test I (<10 mm) and tear-film break-up time (TBUT) <10 seconds in at least one eye performed by an ophthalmologist. Patients with abnormal TBUT and Schirmer test I were selected for the presence of SS. Diagnosis of SS was made according to 2012 ACR classification criteria, which require at least two of three objective features: keratoconjunctivitis sicca with ocular staining score (OSS) ≥ 3 , positive serum anti-SSA/Ro and/or anti-SSB/La or positive rheumatoid factor (RF) plus anti-nuclear antibody (ANA) titer $\geq 1:320$, and LSGB exhibiting focal lymphocytic sialadenitis (FLS) with a focus score ≥ 1 focus/4 mm².¹⁰ sSS was diagnosed by the previous criteria in addition to superimposed rheumatic disease evaluated by a rheumatologist. RA patients were diagnosed according to 2010 ACR-European League Against Rheumatism (EULAR) classification criteria for RA.¹¹ Systemic lupus erythematosus (SLE) patients were diagnosed using 2012 Systemic Lupus International Collaborating Clinics classification criteria.¹² Scleroderma patients were diagnosed by 2013 ACR-EULAR classification criteria for systemic sclerosis.¹³ A complete clinical evaluation for SS was performed, including age, sex, history of dry mouth and other sicca symptoms, salivary-gland enlargement, and symptoms/signs suggestive of disease-related extraglandular manifestations. The approach taken for dry-eye patients for diagnosis of SS is shown in Figure 1.

Ocular staining score

Tests were done to assess the extent of ocular surface damage using rose bengal dye. Scoring was done according to the van Bijsterveld scoring (vBS) system. A score ≥ 3 on vBS is considered abnormal and sufficient to cause the same score on the Sjögren's International Collaborative Clinical Alliance (SICCA) OSS after taking the opinion of a ophthalmologist. Different OSS scores are shown in Figure 2.

Serological tests

Serological tests included ANAs determined by indirect immunofluorescence assay on HEp2 cells (titer $\geq 1/320$ considered positive) and RF detected by latex-agglutination test supplied by Spinreact. Antibodies to the extractable nuclear

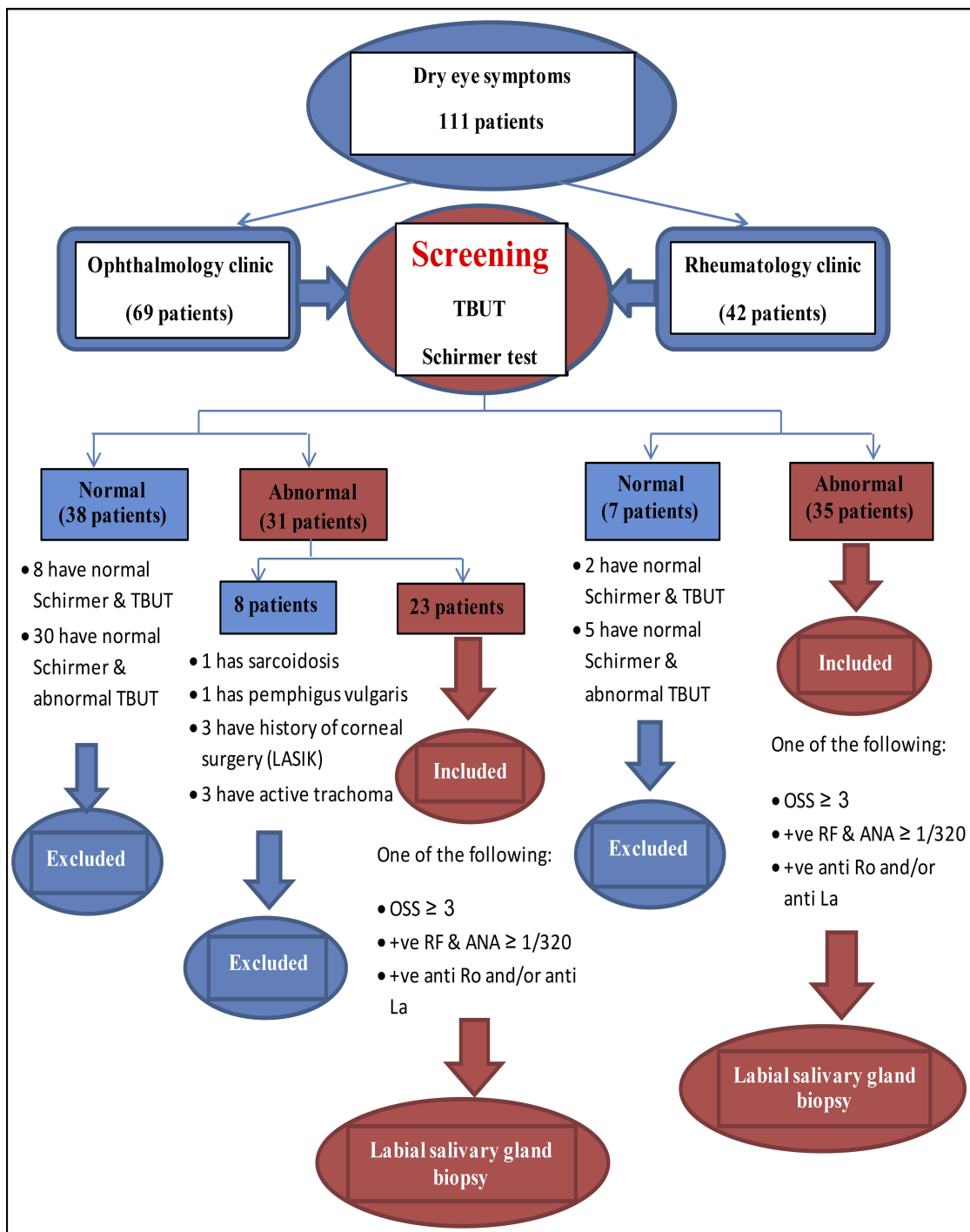


Figure 1 Flowchart for inclusion of dry-eye patients to be included in the study to diagnose Sjögren's syndrome.

Abbreviations: TBUT, tear-film breakup time; OSS, ocular staining score; RF, rheumatoid factor; ANA, antinuclear antibody.

antigens, Ro/SSA and La/SSB, were detected by ELISA (Alegria assay supplied by Orgentec Diagnostika).

Labial salivary–gland biopsy

LSGB was performed in selected patients who had one of OSS ≥ 3 , positive RF and ANA titer $\geq 1/320$, and positive anti-

Ro and/or anti-La. LSGBs were performed after local-anesthetic infiltration to harvest five to ten glands and then fixed in neutral-buffered formalin. Three to five formalin-fixed LSGPs were processed by the pathology department (paraffin embedding, sectioning, and H&E staining). Histological sections were analyzed under light microscopy (Olympus

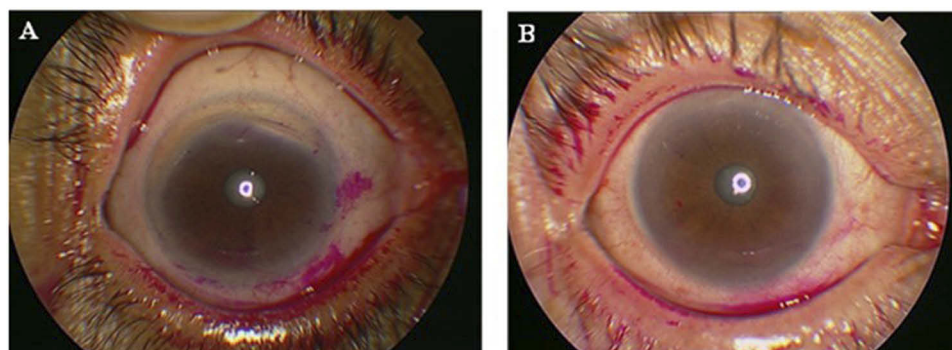


Figure 2 Ocular staining score (OSS). **(A)** OSS with rose bengal dye giving a score >3 . **(B)** OSS with rose bengal dye giving a score <3 .

CX 23L) according to criteria of: number of salivary-gland lobules; percentage of adipose tissue on the salivary glands ($<10\%$ or $>10\%$); absence or presence of ductal dilatation, acinar atrophy, and sclerosis of glandular connective tissue; acinar:ductal ratio (normal ratio — similar to normal glands, reduced ratio — with increased ductal component); the presence of lymphocytic foci (one focus is composed of at least 50 grouped lymphocytes); and ratio number of lobules:number of foci. A positive diagnostic biopsy for SS has been defined as FLS with a focus score ≥ 1 per 4 mm^2 .¹⁴ FLS is identified by the presence of one or more dense aggregates of ≥ 50 lymphocytes (usually several hundred or more lymphocytes), usually located in perivascular or periductal locations, adjacent to normal- appearing mucous acini in gland lobes or lobules lacking duct dilation or interstitial fibrosis, and containing no more than a minority proportion of plasma cells. This diagnosis is assigned when these foci are the only inflammation present in a specimen or the most prominent feature. Focus-score in the setting of FLS is then assigned by assessing the glandular area and calculating the number of lymphocytic foci present per 4 mm^2 of glandular area by an equation (focus score = number of foci $\times 4$ /total glandular area). The total area of H&E-stained thin sections was determined by using the ocular micrometer scale (reticule). A focus score ≥ 1 is diagnostic for SS (Figure 3). Other histopathological features were considered: nonspecific chronic sialadenitis, granulomatous inflammation, lymphoma, or within normal limits (Figure 4).

Statistical analysis

Data collected were coded, tabulated, and statistically analyzed using SPSS 25. Descriptive statistics are given for parametric quantitative data as means \pm SD and for non-parametric quantitative data as medians and IQR, while

categorical data are presented as numbers and percentages. Distribution of the data was assessed by Shapiro–Wilk test.

Analyses were done between the two groups for parametric quantitative data using independent-sample *t*-tests and for nonparametric quantitative data using Mann–Whitney *U* tests. Analyses were done between the two groups for qualitative data using χ^2 tests (expected number per cell >5) and Fisher's exact tests (expected number per cell <5). Correlations between different variables were done using Spearman's ρ correlation coefficient. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were assessed for prediction of SS. The level of significance was $P < 0.05$.

Results

A total of 58 of 111 patients had aqueous-deficient dry eye were included in the current study: 23 (39.7%) in the ophthalmology clinic cohort (group I) and 35 (60.3%) in the rheumatology clinic cohort (group II). There were 52 females (89.7%) and six males (10.3%). Their age ranged from 25 to 75 years with a mean of 44.76 ± 11.7 years. In group II, 30 (85.7%) patients had RA, four (11.4%) had SLE, and one (2.9%) had scleroderma. Patient characteristics are summarized in Table 1. OSSs showed severe ocular surface damage (OSS ≥ 3) in four (17.4%) patients in group I and four (11.4%) patients in group II. Patients in group II had more positive RF compared to group I ($P = 0.002$). ANA was positive in one (4.3%) patient in group I with a titer of 1/40 and one (2.9%) patient in group II with a titer of 1/20. Only one (4.3%) patient from group I had antibodies to SSA/Ro, and none was positive for anti-SSB/La. LSGBs were necessary in seven (12.1%) patients to complete diagnosis of SS according to ACR 2012 criteria. Among the patients in group I, two had

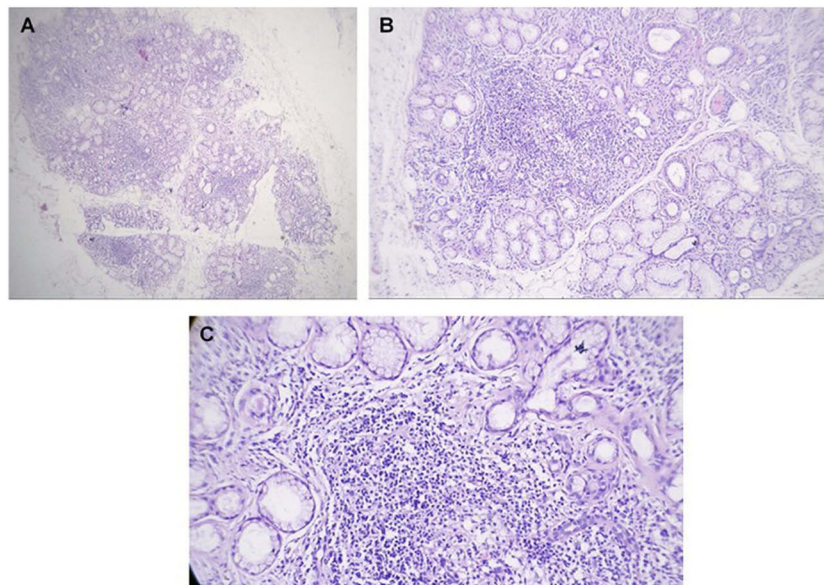


Figure 3 H&E-stained labial salivary glands (LSGs).

Notes: (A) LSGs with three variably sized lymphocytic foci. The entire specimen had a focus score $>1/4 \text{ mm}^2$ (original magnification 40 \times). (B) Normal-appearing acini immediately adjacent to the lymphocytic foci (original magnification 100 \times). (C) LSGs show small lymphocytic aggregate (FLS) that is minimally sized (>50 cells) for inclusion in a focusscore calculation (original magnification 200 \times).

positive LSGBs (focus score ≥ 1), while no patients in group II had a positive biopsy. Figure 5 summarizes the diagnostic flow of the study in SS patients according to ACR criteria.

Frequency of Sjögren's syndrome in dry-eye patients

After application of ACR criteria for SS, three patients had pSS, and its frequency was 13% in the ophthalmology clinic cohort. sSS was not found in our study among the rheumatology clinic cohort. The frequency of SS in all studied dry-eye patients was 5.2%. All SS patients had OSS ≥ 3 , two were positive on biopsy, and one had anti-SSA/Ro. This patient with positive serology developed extraglandular manifestations, including fatigue, constitutional symptoms, arthralgia, and arthritis. RF and ANA were not detected in SS patients.

Comparison between Sjögren's and non-Sjögren's patients

Table 2 compares objective tests in patients with SS and non-SS. SS patients had more severe ocular dryness on Schirmer test ($P=0.007$) and OSS ($P=0.002$). SS patients more frequently displayed LSGBs compatible with SS (FLS ≥ 1 , $P=0.048$). Comparison of autoantibodies between SS and non-SS patients did not show statistical significance.

Diagnostic values of ocular tests and different ACR parameters

Tables 3 and 4 show the results of such-and-such analysis. Schirmer's and the OSS were the most sensitive tests and produced similar sensitivity of 100%, but the OSS was more specific for diagnosis of SS, with specificity of 90.9% compared to 83.6% for the Schirmer test. In addition, OSS had the highest positive and negative predictive values (37.5% and 100%, respectively). TBUT had lower sensitivity (33.3%) and specificity (56.4%). Schirmer test and OSS were significantly positively correlated with SS ($P<0.001$ for each). Anti-SSA/Ro antibody produced the highest sensitivity (33.3%), specificity (100%), positive predictive value (100%), and negative predictive value (96.5%) for SS diagnosis compared to RF and ANA. Anti-SSA/Ro was significantly positively correlated with SS ($P<0.001$). LSGB exhibiting FLS focus score ≥ 1 was the most accurate for SS diagnosis, with sensitivity, specificity, and positive and negative predictive values of 100% and showing a significant positive correlation with SS ($P<0.001$).

Discussion

Diagnosis of SS is difficult and complex. There is no single diagnostic test with satisfactory validity. In clinical settings, it is not common for ophthalmologists to screen

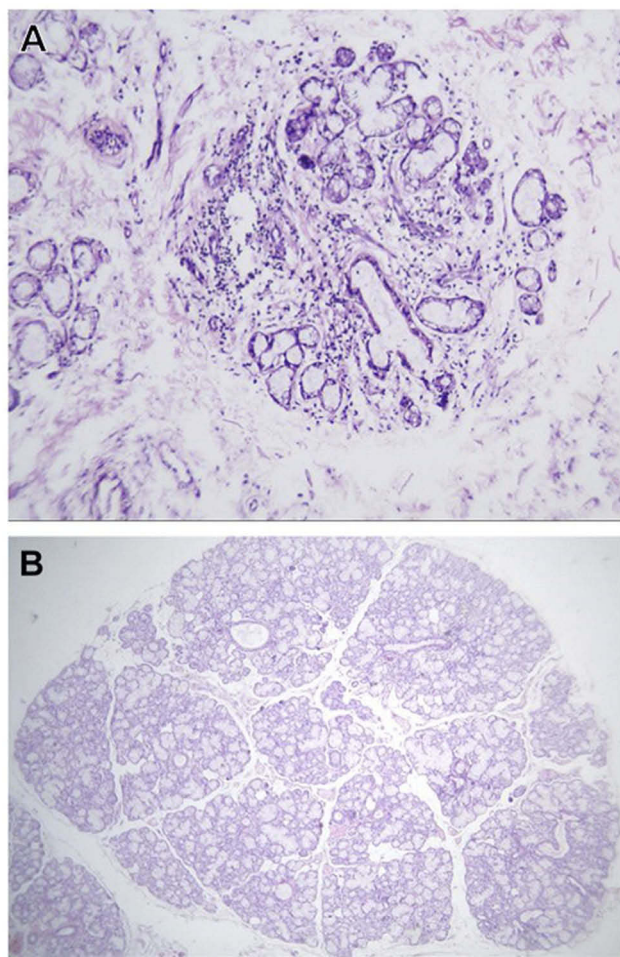


Figure 4 H&E-stained labial salivary glands (LSGs).

Notes: (A) LSGs exhibiting nonspecific chronic sialadenitis with scattered lymphocytes and plasma cells (original magnification 100×). (B) LSGs exhibiting normal glands (original magnification 40×).

for SS among dry-eye patients, because extraglandular involvement is not very frequent and ophthalmologists are not familiar with systemic extraglandular manifestations. Different classification criteria have been set for diagnosis; however, the ACR 2012 classification includes three objective measures that can simplify the diagnosis.¹⁰

In the present study, three (5.2%) of 58 dry-eye patients had SS. They were pSS, resulting in a frequency of 11.4% in the ophthalmology clinic cohort. sSS was not detected in the studied patients. Other studies have reported different frequencies of SS among dry-eye patients. Akpek et al reported that of 220 patients with dry eye, 24 (10.9%) patients had pSS.⁶ Zhang et al studied the prevalence of SS in 327 patients with aqueous-deficient dry eye. They reported that 21 (6.4%) had pSS and 17 (5.2%) had sSS.¹⁵ Lee et al observed that SS was present in 58 (28%) of all dryeye patients and 39 (19%)

patients showed pSS.¹⁶ Kan et al found that 14 of 45 dry-eye patients (31.1%) had pSS.¹⁷ Henrich et al found that the frequency of pSS in 228 dry-eye patients was 11%.¹⁸ Yen et al found incidence of developing SS of 4.8% for DES patients.¹⁹ These differences in frequency may be due to different study populations and use of different criteria for SS diagnosis.

The OSS (a parameter of the ACR) showed the best ratio of specificity (90.9%) to sensitivity (100%) for SS diagnosis, followed by Schirmer test (specificity 83.6% and sensitivity 100%). Both tests were significantly positively correlated with SS ($P < 0.001$). TBUT had poor diagnostic value (33.3% sensitivity and 56.4% specificity). In agreement with other results, Versura et al proved that OSS (lissamine green staining) had the best diagnostic performance for SS (sensitivity 0.63 and specificity 0.89) and TBUT had poor diagnostic performance (sensitivity 0.92 and specificity 0.17). Conversely, they found that the Schirmer test showed poor diagnostic performance (sensitivity 0.42 and specificity 0.76).²⁰ Contrary to our results, Akpek et al found the severity of DES measured by Schirmer test, TBUT, and OSS did not correlate with a diagnosis of SS.⁶

It has been shown that autoantibodies may be present before the onset of SS symptoms, as found in Jonsson et al and Theander et al,^{21,22} however, our study reported low frequency of autoantibodies in studied patients. This could be explained with different reasons. First, autoantibody positivity is associated with more active and systemic disease.²³ Second, the presence of SSA/Ro antibodies is associated with a higher risk of extraglandular manifestations.⁶ Last, follow-up of pSS patients while seronegative has shown they remain polysymptomatic. Further, 39% of these seronegative patients were given revised diagnoses over the followup, which included RA, SLE, mixed connective-tissue disease, and scleroderma.²⁴ The diagnostic value of autoantibodies in this study showed that anti-SSA/Ro antibody was the most accurate serological test, producing sensitivity of 33.3%, specificity 100%, PPV 100%, and NPV 96.5%. The correlation of SS with autoantibodies showed a significant positive correlation with anti-SSA/Ro ($P < 0.001$), but not with other antibodies. Similarly, Theander et al found that anti-SSA/Ro was 51% sensitive and 98% specific for pSS diagnosis. However, the predictive value for developing pSS was highest for anti-SSB/La.²² In disagreement with our results, Solomon et al reported the average sensitivity of ANA in SS was 48% and specificity 52%.²⁵ ACR

Table I Characteristics of dry-eye patients studied

	Group I: ophthalmology clinic cohort (n=23)	Group II: rheumatology clinic cohort (n=35)	t/U/χ^2	P-value
Age, years, mean (SD)	44.2 (14.3)	45.1 (9.9)	-0.263	0.794
Sex				
Male, n (%)	3 (13%)	3 (8.6%)	0.299 ^b	0.673
Female, n (%)	20 (87%)	32 (91.4%)		
Dry eye, n (%)	23 (100%)	35 (100%)	0	0
Dry-eye duration, years, median/IQR	1/(0.3–2)	1/(0.3–3)	388	0.816
Dry mouth, n (%)	20 (87%)	29 (82.9%)	0.178 ^b	1
Dry-mouth duration, years, median/IQR	1/(0.2–2.8)	1/(0.2–2)	264	0.593
Salivary-gland enlargement, n (%)	2 (8.7%)	3 (8.6%)	0 ^(b)	1
Schirmer test I				
<5 mm, n (%)	3 (13%)	9 (25.7%)	1.358 ^b	0.329
5–10 mm, n (%)	20 (87%)	26 (74.3%)		
TBUT				
<5 seconds, n (%)	9 (39.1%)	16 (45.7%)	0.245 ^a	0.620
5–10 seconds, n (%)	14 (60.9%)	19 (54.3%)		
OSS				
≥3, n (%)	4 (17.4%)	4 (11.4%)	0.415 ^b	0.700
<3, n (%)	19 (82.6%)	31 (88.6%)		
ANAs, n (%)	1 (4.3%)	1 (2.9%)	0.093 ^b	1
RF, n (%)	0	12 (34.3%)	9.943 ^b	0.002*
Anti-SSA/Ro, n(%)	1 (4.3%)	0	1.548 ^b	0.397
Anti-SSB/La, n (%)	0	0	0	0
Histopathology of LSGB	n=3	n=4	4.273 ^b	0.486
FLS (focus score ≥1)	2 (66.7%)	0		
FLS (focus score <1)	1 (33.3%)	2 (50%)		
Chronic nonspecific sialadenitis	0	1 (25%)		
Normal	0	1 (25%)		

Notes: Parametric quantitative data expressed as means (SD) and nonparametric quantitative data expressed as medians (IQR), while qualitative data are expressed as numbers and percentages. Independent-sample t-tests for parametric quantitative data between the two groups; Mann–Whitney U test for nonparametric quantitative data between the two groups. ^a χ^2 test (if expected value within cell >5); ^bFisher's exact test (if expected value within cell <5) for qualitative data between the two groups. *P<0.05. **Abbreviations:** OSS, ocular staining score; TBUT, tear-film breakup time; ANAs, antinuclear antibodies; RF, rheumatoid factor; FLS, focal lymphocytic sialadenitis; LSGB, labial salivary-gland biopsy.

classification by Shiboski et al showed that combined positive RF and ANA titer of $\geq 1/320$ had reasonable specificity, but low sensitivity for SS diagnosis. They also found that anti-Ro and/or anti-La had the highest sensitivity and specificity.¹⁰ Akpek et al found that SS was significantly correlated with autoantibodies, not only

with anti-Ro but also anti-La, ANA and RF.⁶ In Zhang et al, pSS was significantly more likely to occur in patients with positive ANA and RF.¹⁵

In the present study, positive LSGB allowed for a definitive diagnosis of SS, resulting in sensitivity, specificity, PPV, and NPV of 100%. There was also a significant

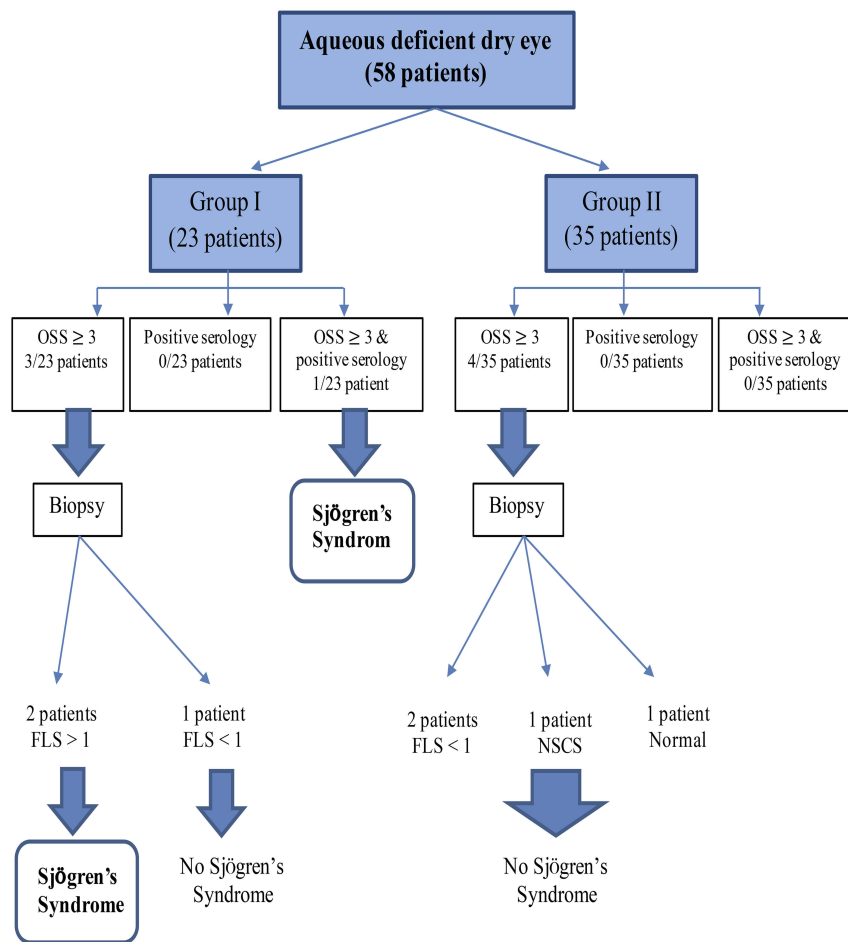


Figure 5 Diagnostic flow of study in Sjögren's syndrome patients.
Abbreviations: OSS, ocular staining score; FLS, focal lymphocytic sialadenitis; NSCS, nonspecific chronic sialadenitis.

Table 2 Comparisons of ocular tests, autoantibodies, and LSGB with Sjögren's syndrome

		Sjögren's		P-value
		Negative	Positive	
		n=55	n=3	
Schirmer test	5–10 mm <5 mm	46 (83.6%) 9(16.4%)	0 3 (100%)	0.007*
TBUT	5–10 sec <5 sec	31 (56.4%) 24(43.6%)	2(66.7%) 1 (33.3%)	1
OSS	<3 >3	50 (90.9%) 5(9.1%)	0 3 (100%)	0.002*
RF	Negative Positive	43 (78.2%) 12(21.8%)	3(100%) 0	1
ANAs	Negative Positive	53 (96.4%) 2(3.6%)	3(100%) 0	1

(Continued)

Table 2 (Continued).

		Sjögren's		P-value
		Negative	Positive	
		n=55	n=3	
Anti-SSA/Ro	Negative Positive	55 (100%) 0	2(66.7%) 1 (33.3%)	0.052
LSGB	Negative Positive	n=5 5 (100%) 0	n=2 0 2 (100%)	0.048*

Notes: Qualitative data expressed as numbers and percentages. Fisher's exact test (if expected value within cell <5) for qualitative data between the two groups. * $P<0.05$.
Abbreviations: TBUT, tear-film breakup time; OSS, ocular staining score; RF, rheumatoid factor; ANAs, antinuclear antibodies; LSGB, labial salivary-gland biopsy.

Table 3 Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ocular tests, autoantibodies and LSGB for diagnosis of Sjögren's syndrome

	Sensitivity	Specificity	PPV	NPV	Accuracy
Schirmer test <5 mm	100%	83.6%	25%	100%	84.5
TBUT <5 seconds	33.3%	56.4%	4%	93.9%	55.2
OSS ≥ 3	100%	90.9%	37.5%	100%	91.4
RF	0	78.2%	0	93.5%	74.1
ANAs	0	96.4%	0	94.6%	91.4
Anti-SSA/Ro	33.3%	100%	100%	96.5%	96.6
LSGB	100%	100%	100%	100%	100

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; TBUT, tear-film breakup time; OSS, ocular staining score; RF, rheumatoid factor; ANAs, antinuclear antibodies; LSGB, labial salivary-gland biopsy.

Table 4 Correlations between ocular tests, autoantibodies, LSGB, and Sjögren's syndrome

	Sjögren's syndrome	
	r	P-value
Schirmer test	0.457	<0.001*
TBUT	-0.046	0.731
OSS	0.584	<0.001*
RF	-0.119	0.372
ANAs	-0.044	0.742
Anti-SSA/Ro	0.567	<0.001*
LSGB	0.828	<0.001*

Notes: Nonparametric Spearman's ρ correlation. * $P<0.05$.

Abbreviations: TBUT, tear-film breakup time; OSS, ocular staining score; RF, rheumatoid factor; ANAs, antinuclear antibodies; LSGB, labial salivary-gland biopsy.

positive correlation between LSGB and SS ($P<0.001$). As in previous studies, LSGB was considered the most accurate for diagnosis of SS. Guellec et al reported the sensitivity of LSGB ranged from 63.5% to 93.7% and specificity from 61.2% to 100%.²⁶ Giovelli et al found that LSGB had high diagnostic value, with sensitivity 86.57%, specificity 97.43%, PPV 95%, and NPV 92.6%.²⁷ Wicheta et al

showed the sensitivity of LSGB was 82.3%, specificity 90%, PPV 66.6%, and NPV 95.4%.²⁸ Another study of Wicheta et al found that a positive LSGB result allowed for a definitive diagnosis of SS in 80% of biopsied patients.²⁹

There are some limitations of our study. The diagnostic values of objective tests for diagnosis of SS are not accurate, due to small number of SS patients detected in this study, LSGBs being performed for only seven patients. Assessment of keratoconjunctivitis sicca was done by vBS (maximum score 9) instead of SICCA OSS (maximum score 12). Accordingly, some patients who had negative vBS might have had positive SICCA OSS, so they might have been missed for SS diagnosis. There are no studies validating the conversion of SICCA score with the traditional vBS technique.³⁰ Another problem is lack of use of ultrasound of salivary glands, which has proved to be a simple noninvasive method for early diagnosis of SS with high diagnostic value.^{31,32} Also, the inability to use tests for detection of novel antibodies, including anti-SP1, anti-CA6, and anti-PSP was a drawback. These

autoantibodies were recently involved in SS diagnosis, particularly in the early stage of disease.^{33–35}

Conclusion

SS was detected with reasonable frequency among dry-eye patients, particularly pSS. Screening of DES for SS can pick patients of SS early in the disease course. We recommend that clinical evaluation, ocular tests, and serological analysis be performed with any dry-eye patient for early diagnosis of SS.

Disclosure

The authors report no conflicts of interest in this work.

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