

Validity of Screening Tests for Sjögren's Syndrome in Ambulatory Patients with Chronic Diseases

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ABSTRACT. Objective. To determine the validity of screening tests for Sjögren's syndrome (SS) in ambulatory patients with chronic diseases.

Methods. Three hundred randomly selected patients from the rheumatology and internal medicine clinics of a tertiary care center were assessed for SS according to the American-European Consensus Group criteria. During the screening phase, an interview, the European questionnaire for sicca symptoms, Schirmer-I test, and the wafer test were carried out in all patients. Patients with positive screening had confirmatory tests including fluorescein staining test, nonstimulated whole salivary flow, and autoantibody testing. Confirmatory tests were also done in 13 patients with negative screening. During the last phase, lip biopsy was proposed to patients who met preestablished criteria.

Results. Women made up 79% of the study population. Mean age of subjects was 42.8 ± 15.7 years. Two hundred twenty patients (73%) had positive screening. The distribution of positive test results was: xerophthalmia 118 (39%), xerostomia 103 (34%), Schirmer-I test 101 (34%), and wafer test 187 (62%) patients met criteria for SS. All screening tests were useful for identifying patients with SS; however, the model composed of at least one positive response to the European questionnaire (EQ₁), Schirmer-I test, and wafer test showed the best performance.

Conclusion. Use of the European questionnaire, Schirmer-I test, and wafer test in parallel was useful for identifying patients with SS among ambulatory patients with chronic diseases. (First Release Mar 15 2006; J Rheumatol 2006;33:907-11)

Key Indexing Terms:
SJÖGREN'S SYNDROME

SCREENING

Sjögren's syndrome (SS) refers to keratoconjunctivitis sicca and decreased salivary flow resulting from lymphocytes that infiltrate the lacrimal and salivary glands¹. The prevalence of SS in 2 population studies conducted in Greece was 3.6% and 4.8%, respectively^{2,3}; a similar percentage was reported in Sweden, 2.7%⁴, and in a population-based survey conducted in Manchester, UK, 3% to 4%, among subjects aged 18-75 years⁵. In ambulatory patients attending a tertiary care center, SS was diagnosed in 13%⁶.

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Although SS has been considered the most common connective tissue disease, epidemiological data are scarce, because of the heterogeneity of the populations studied, the use of different tests for the evaluation of lacrimal and salivary function, and use of different classification criteria. Several tests have been proposed for the evaluation of lacrimal and salivary gland involvement in subjects with SS. Their performance in patients with SS and controls has been adequate^{7,8}; however, in the general population their predictive value has been weak⁹. Their utility among ambulatory patients with chronic diseases in whom the presence of SS is unknown, a population that most likely reflects the anticipated clinical use of these tests, still needs to be determined. This is the aim of our study.

MATERIALS AND METHODS

A total of 336 patients were selected using random numbers from the rheumatology and internal medicine clinics of a tertiary care center. Thirty-six declined to participate, therefore 300 were included in the study.

Subjects who had taken any medication that may reduce salivary flow (i.e., antihistamines, sedatives, β -blockers, diuretics, etc.) within 48 hours before the study were excluded. All participants were asked to refrain from eating, drinking, smoking tobacco, chewing, and oral hygiene procedures for at least 1 hour before the study. Subjects were seen in a closed room with no air-conditioning or heating, between 8:00 and 11:00 A.M.

The study was designed in 3 phases: screening, confirmatory tests, and lip biopsy (Figure 1). During the screening phase, all patients had a face-to-face interview with a single physician, blinded to the medical diagnoses, using a

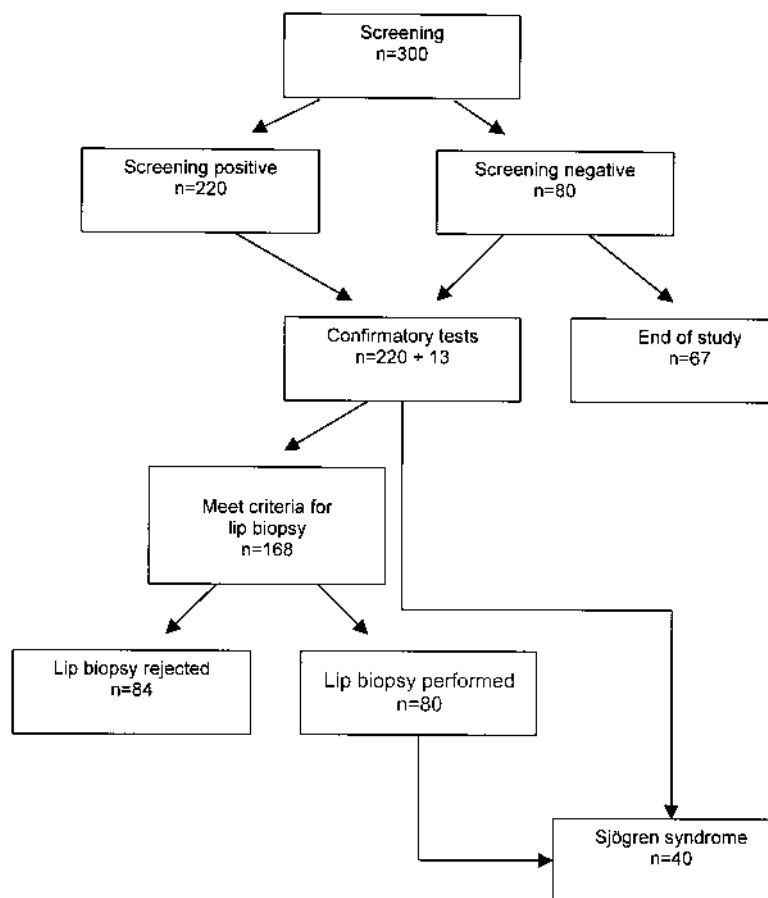


Figure 1. The selection of the study population.

standardized form that included questions about demographic data, health-related behaviors, and use of medications. In addition, a validated screening questionnaire for sicca symptoms^{10,11}, the Schirmer-I test¹², and the wafer test¹¹ were carried out. Patients with at least one affirmative response to the screening questionnaire, Schirmer-I test ≤ 5 mm in 5 min, or wafer test > 4 min were considered to have a positive screening result.

In the second phase of the study, patients with positive screening underwent confirmatory tests including the fluorescein staining test, nonstimulated whole salivary flow rate (NSWSF), and autoantibody tests. Confirmatory tests were also done in a random sample of 15% of patients with negative screening.

During the last phase of the study, a lip biopsy was proposed to all patients who had ≥ 2 of the following results: at least one affirmative answer to the oral component of the screening questionnaire, wafer test > 4 min, presence of keratitis by the fluorescein staining test, NSWSF < 0.3 ml/min, and positive anti-Ro and/or anti-La antibodies.

Screening tests

Questionnaire. A validated 6-item screening questionnaire for sicca symptoms^{10,11} was self-administered. The questionnaire was considered positive if at least one question was answered affirmatively (EQ₁).

Schirmer-I test. The Schirmer-I test was done as described¹², using 2 standardized sterile filter paper strips (Sno strips; Chauvin Pharmaceuticals, Romford, UK). We considered the test as positive if the moistened area was ≤ 5 mm in 5 min in at least one eye.

Wafer test. The wafer test was done as described¹¹. Time of dissolution of the wafer, as measured from the moment the wafer was put on the tongue until it had dissolved, was the main outcome. The test was considered positive if the time of dissolution of the wafer was > 4 min.

Confirmatory tests

Eye evaluation. The corneal surface condition was evaluated by an ophthalmologist, using fluorescein staining test. The ophthalmologist was unaware of the results of the screening procedure and the patients' diagnoses.

Nonstimulated whole saliva flow collection. NSWSF was measured by the spitting method¹³. Saliva was collected for a period of 5 min^{9,13} and the volume expressed in ml/min.

Autoantibody tests. A blood sample was drawn and serum was stored at -70°C for autoantibody testing at the end of the second phase. Rheumatoid factor was tested by nephelometry; antinuclear antibodies by indirect immunofluorescence using HEp-2 cells as substrate; and serum antibodies to Ro/SSA and La/SSB were tested by ELISA.

Lip biopsy. Minor salivary glands were obtained through normal-appearing mucosa by an oral surgeon. Biopsy specimens contained 2 to 10 glands (median 5); 90% of the specimens contained 4 to 7 glands. The area of the gland tissue was measured with a 10×10 mm graticule at $40\times$ magnification. All biopsies were evaluated by an expert pathologist, blinded to previous results and medical diagnosis. Focal lymphocytic sialoadenitis was diagnosed with a focus score ≥ 1 , defined as number of lymphocytic foci containing > 50 lymphocytes per 4 mm^2 of glandular tissue^{14,15}.

Definitions. The following definitions are used in this report: EQ₁ refers to one or more affirmative answers to the screening questionnaire; xerophthalmia refers to one or more affirmative answers to the ocular component of the screening questionnaire; xerostomia refers to one or more affirmative answers to the oral component of the screening questionnaire; xerophthalmia and xerostomia refer to one or more affirmative answers to the ocular and oral components of the screening questionnaire. Decreased salivary flow refers to

salivary flow rate ≤ 0.1 ml/min¹⁶; keratoconjunctivitis sicca was diagnosed with the fluorescein staining test¹⁴. SS was defined according to the criteria proposed by the American-European Consensus Group (AECG)¹⁴.

The study was conducted in a tertiary care center, where most patients are admitted or referred for specialized care due to complex diseases. The rheumatology clinic provides regular care to 5942 patients (mean age 48.8 yrs, 85.5% female); 4813 (81.0%) have connective tissue disease diagnoses. The internal medicine clinic provides regular care to 10,314 patients (70.0% female).

Statistical analysis. Descriptive statistics were used to define the subjects' characteristics in each group. Categorical variables were compared using chi-square or Fisher's exact test and continuous variables were analyzed using Student's t test. The validity of the screening tests for SS was estimated using 2×2 tables. We calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, which was defined as the proportion of patients correctly classified as having or not having SS, given that the screening tests were positive or negative. PPV and NPV were calculated according to the prevalence for SS seen in the study population. The likelihood ratio and 95% confidence intervals (95% CI) were calculated for the screening tests as sensitivity/(1 - specificity), and can be interpreted as the increased likelihood of having SS, given the positive screening. P value was set at < 0.05 , 2-tailed. Analysis was performed using Stata 5.0 (Stata Corp., College Station, TX, USA).

The study was approved by our Institutional Committee of Biomedical Research and all patients provided signed informed consent.

RESULTS

Population characteristics. Characteristics of the study population were as described⁶; 300 patients (female 79%, mean age 42.8 ± 15.7 yrs) were included.

Patients' diagnoses in rheumatology were mostly rheumatoid arthritis or systemic lupus erythematosus (76%) and other connective tissue diseases (9%), and in internal medicine endocrine diseases, systemic arterial hypertension, obesity, and peptic disorders (61%); only 15% of patients had rheumatic disorders.

Screening. Two-hundred twenty patients (73%) were positive to screening (Figure 1). The distribution of test results was as follows: EQ₁ 146 (49%), xerophthalmia 118 (39%), xerostomia 103 (34%), xerophthalmia and xerostomia 74 (25%), Schirmer-I test ≤ 5 mm 101 (34%), Both eyes, n (%) 67 (22.3), Wafer test < 4 min, n (%) 187 (62%)

mia 103 (34%), xerophthalmia and xerostomia 74 (25%), Schirmer-I test 101 (34%), and the wafer test 187 (62%) patients (Table 1).

Prevalence of keratoconjunctivitis sicca and decreased salivary flow. Among the 220 patients with positive screening plus 13 with negative screening (Figure 1), confirmatory tests were carried out as follows: fluorescein staining test 216, NSWSF 227, anti-Ro/SSA and anti-La/SSB 216 patients. Fifty-five (26%) patients were diagnosed with keratoconjunctivitis sicca, 28 (12%) with decreased salivary flow, and 39 (18%) tested positive for anti-Ro/SSA or anti-La/SSB antibodies (Table 2).

Prevalence of SS. One hundred sixty-eight patients met the criteria for lip biopsy. Eighty-eight patients declined the procedure and biopsy was performed in 80 (48%). In 39 (49%) patients, lip biopsy showed focal sialoadenitis; however, only 28 patients fulfilled the criteria for SS. Twelve additional patients met the criteria for SS although the lip biopsy was not performed or did not show focal sialoadenitis; therefore 40 (13%) patients were classified as having SS (Figure 1).

Validity of screening tests to identify patients with SS. Comparing diverse models including the screening questionnaire and the Schirmer-I and wafer tests, the best performance in terms of prediction was achieved by combined use of EQ₁, positive Schirmer-I and wafer tests, with a likelihood ratio of 9.4 (95% CI 6.0, 14.7). This model was significantly better than the use of EQ₁, xerophthalmia and xerostomia, and positive Schirmer-I and wafer tests (Table 3).

DISCUSSION

The European questionnaire, the Schirmer-I test, and the wafer test performed well in identifying SS among ambulatory patients with chronic diseases. These tests have been proposed to be useful for screening subjects with lacrimal and salivary gland dysfunction^{10,11}.

Table 1. Results of the screening tests in the study population.

Test	Total Population	Rheumatology, Internal Medicine,		p*
		n = 181	n = 119	
European questionnaire				
EQ ₁ ** , n (%)	146 (49)	99 (55)	47 (40)	0.01
Xerophthalmia***, n (%)	118 (39)	81 (45)	37 (31)	0.02
Xerostomia†, n (%)	103 (34)	77 (43)	26 (22)	< 0.001
Xerophthalmia and xerostomia††, n (%)	74 (25)	59 (33)	15 (13)	< 0.001
Schirmer-I test ≤ 5 mm				
One eye, n (%)	101 (34)	79 (44)	22 (18)	< 0.001
Both eyes, n (%)	67 (22.3)	57 (31.5)	10 (8.4)	< 0.001
Wafer test < 4 min, n (%)	187 (62)	118 (65)	69 (58)	0.24

* Comparison between patients from rheumatology and internal medicine. ** EQ₁: ≥ 1 affirmative answer to the screening questionnaire. *** Xerophthalmia: ≥ 1 affirmative answer to the ocular component of the screening questionnaire. † Xerostomia: ≥ 1 affirmative answer to the oral component of the screening questionnaire. †† Xerophthalmia and xerostomia: ≥ 1 affirmative answer to the ocular and oral component of the screening questionnaire.

Table 2. Prevalence of keratoconjunctivitis sicca, decreased salivary flow, and Sjögren's syndrome (SS).

	Study Population	Rheumatology	Internal Medicine	p*
Keratoconjunctivitis sicca [†] , n (%)	55 (26)	47 (34)	8 (10)	< 0.001
Decreased salivary flow [†] , n (%)	28 (12)	21 (15)	7 (8)	0.28
SS ^{††} , n (%)	40 (13)	35 (19)	5 (4)	< 0.001

* Comparison between rheumatology and internal medicine population. [†] Confirmatory tests as follows (study population/rheumatology/internal medicine): fluorescein staining test (216/138/78), nonstimulated whole salivary flow rate (227/144/83). ^{††} Estimated in the total population.

Table 3. Validity of screening tests for Sjögren's syndrome.

	Sensitivity	Specificity	PPV	NPV	Positive Likelihood Ratio (95% CI)	Accuracy
EQ ₁	0.98	0.59	0.27	0.99	2.4 (2.1, 2.8)	0.64
Xerophthalmia + xerostomia	0.68	0.82	0.37	0.94	3.8 (2.7, 5.3)	0.80
Schirmer-I test + wafer test	0.77	0.82	0.40	0.95	4.3 (3.1, 5.9)	0.82
EQ ₁ + Schirmer-I test + wafer test	0.75	0.92	0.59	0.96	9.4 (6.0, 14.7)	0.90
Xerophthalmia + xerostomia + Schirmer-I test + wafer test	0.55	0.95	0.65	0.93	11.0 (5.9, 20.4)	0.90

PPV: positive predictive value, NPV: negative predictive value.

Participating patients were chosen randomly and studied using a structured approach. The screening tests were administered in parallel to all.

The prevalence of xerophthalmia, xerostomia, and positive Schirmer-I test we found is similar to that reported among 636 patients with rheumatoid arthritis from the Oslo Rheumatoid Arthritis Register¹⁷, using a similar approach, and higher than that found in a population-based study in Manchester, UK⁹. No data estimates exist for the wafer test.

Confirmatory tests were carried out in the patients with positive screening. Keratoconjunctivitis sicca was diagnosed with the fluorescein staining test and decreased salivary flow with the NSWSF rate. Saliva was collected by the spitting method for 5 minutes, a method shown to be reproducible and reliable^{9,13}. We standardized saliva collection for body position, time of day, time since last major oral stimuli, and exposure to light and olfactory stimuli; however, it is not known if talking during the interview had any effect on saliva production and consequently on the wafer test result and NSWSF rate. The prevalence of decreased salivary flow detected among patients in internal medicine is similar to that reported in disease controls with no SS from the European Community Study Group⁷, and the estimate derived from patients in rheumatology agrees with that from the Oslo Rheumatoid Arthritis Register¹⁷.

SS was defined according to the criteria proposed by the AECG¹⁴, which probably represents the best instrument currently available for classification of patients with this disease. Thus we consider that ascertainment of lacrimal and salivary gland dysfunction and of patients with SS was appropriate.

The study was conducted in a tertiary care center. Participants from the rheumatology clinic were of similar age,

sex, and diagnoses to the whole population of patients attending this clinic. Patients from the internal medicine clinic had a sex distribution similar to the whole population of patients at that clinic; unfortunately, we do not have a detailed registry of age and diagnoses from that clinic. Nevertheless, we consider that our results apply to the ambulatory patients with chronic diseases seen in our hospital.

All screening instruments were valid to identify patients with SS. The best predictive model included EQ₁, Schirmer-I, and wafer tests. Given the suitability, ease of administration, low cost, and minimal discomfort of the tests, we would recommend their use in parallel to identify SS in ambulatory patients with chronic diseases.

Few studies have assessed the validity of screening tests for SS. In a population-based study, a weak association between subjective symptoms of and objective testing for dry eyes and dry mouth was found⁹. In hospital settings among patients with well defined health status and where presence of SS was known, the screening tests performed well^{7,8}. In this scenario, estimates of sensitivity and specificity of the tests tend to overestimate their effectiveness, since any test can perform well if the task is to distinguish between the very sick and the very well. The different performance of screening tests in population-based studies and hospital settings is explained by several factors, including a higher prevalence of and full spectrum of SS among the patients than in the general population, and an expected better standardization of the tests and precision of measurements in hospital settings. These methodological and practical problems influence the level of association between screening tests and SS in different scenarios.

Our results demonstrate the performance of the tests in

patients with a spectrum of disease that most likely reflects their anticipated clinical use. Our results support the validity of the European questionnaire as a screening tool for SS^{7,10}.

Some potential limitations of our study need to be considered. Lip biopsy was rejected by half the patients. It is expected that some of these patients might have SS and in the analyses they were classified as non-SS. This potential misclassification would result in underestimation of the prevalence of SS and the PPV reported; however, the sensitivity, specificity, NPV, likelihood ratio, and accuracy described for each model would not vary, therefore this limitation does not affect our results significantly. This was a single-center study, and whether our results apply to patients with chronic diseases from other tertiary care centers needs to be determined. The study was conducted in a center with an expected higher prevalence of SS than in primary care clinics and the general population: in this situation the effectiveness of the tests would be overestimated. As a consequence, the validity of the screening tests would be different in primary care clinics, and their use in the community cannot be addressed directly, except in very general terms. The mean age of the study population was 42 years, therefore we must be cautious in extrapolating these results to elderly populations.

Some strengths of the study are as follows: the validation process was conducted in a population that most likely reflects the real use of the tests. Patients were randomly selected and their SS status was unknown. All patients were studied using a structured approach; SS was diagnosed according to probably the best possible instrument available for classification of patients with this disease.

From our results, we conclude that the use of the European questionnaire, the Schirmer-I test, and the wafer test in parallel is reliable for identifying SS among ambulatory patients attending a tertiary care center.

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