Sjögren's syndrome: a stepwise approach to the use of diagnostic tests

Joaquim Coll, Miquel Porta, Juan Rubiés-Prat, Juan Gutiérrez-Cebollada, Santiago Tomás

Abstract

One hundred and forty two patients (62 with definite Sjögren's syndrome, 24 with probable Sjögren's syndrome, and 56 in whom Sjögren's syndrome was finally ruled out) were studied. Schirmer's test and rose bengal staining for the diagnosis of keratoconjunctivitis sicca and salivary scintigraphy and a labial biopsy sample for the diagnosis of xerostomia were studied in all patients. Rose bengal staining showed high specificity (98%) but low sensitivity (55%). All patients with positive rose bengal staining results had associated xerostomia. In the rose bengal staining positive patients, scintigraphy had 100% specificity. A labial biopsy sample showed high sensitivity in the rose bengal staining, salivary scintigraphy positive group, and high specificity in the rose bengal staining positive, salivary scintigraphy negative group. In patients with negative rose bengal staining, salivary scintigraphy showed 96% specificity and 36% sensitivity. A labial biopsy sample had a sensitivity and specificity greater than 90% in rose bengal staining negative patients. Only 29 biopsy samples were needed to achieve a diagnosis of Sjögren's syndrome in 142 patients (20%). Hence the suggested approach may make it unnecessary to take biopsy samples in approximately 80% of patients with suspected Sjögren's syndrome. Using the stepwise approach of first rose bengal staining, then salivary scintigraphy, and eventually a labial biopsy sample in patients with suspected Sjögren's syndrome, the diagnosis is relatively simple.

Department of Medicine, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain
J Coll
J Rubiés-Prat
J Gutiérrez-Cebollada
S Tomás

Department of Epidemiology, Institut Municipal d'Investigació Mèdica, Universitat Autònoma de Barcelona, Barcelona, Spain
M Porta

Correspondence to: Professor J Coll, Department of Medicine, Hospital del Mar, Passeig Martítim 25–29, E-08003 Barcelona, Spain.

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Primary Sjögren's syndrome is a clinical disease characterised by keratoconjunctivitis sicca and xerostomia with autoimmune processes.[1] When the syndrome is associated with an established autoimmune disease, the term secondary Sjögren's syndrome is used.[2 3] For the diagnosis of Sjögren's syndrome, the presence of xerostomia or keratoconjunctivitis sicca, or both, is necessary.[4] There is currently no general agreement, however, on criteria for the diagnosis of Sjögren's syndrome.

Studies on Sjögren's syndrome have furthered our understanding of autoimmune diseases[5] and of their possible association with some retroviruses.[6 7] As no specific serological markers exist for the disease, the diagnosis must currently rely on auxiliary tests for keratoconjunctivitis sicca and xerostomia.

The aim of this work was to assess the clinical usefulness of a stepwise approach to establishing the diagnosis of Sjögren's syndrome.

Patients and methods

One hundred and forty two patients (121 women and 21 men), aged 35–78 years, consecutively diagnosed in the department of medicine as having the following definite diseases were included in this study: rheumatoid arthritis (46), systemic scleroderma (13), primary biliary cirrhosis (14), liver disease other than primary biliary cirrhosis (8), other autoimmune diseases (10, including three with systemic lupus erythematosus), and primary Sjögren's syndrome (15). Thirty six patients with clinically suspected Sjögren's syndrome were also included in the study.

The following exploratory investigation was performed in all patients. Objective evidence of keratoconjunctivitis sicca was obtained with standard techniques. A type I Schirmer's test was performed by application to the conjunctiva of a No 41 Whatman-type millimetric filter paper. Humidification of less than 5 mm in both eyes was required for a test result to be considered abnormal. Rose bengal staining was carried out by conjunctival instillation of a 1% solution of the dye, and Holm's criteria were followed with grades A and B staining being defined as abnormal.[8] Keratoconjunctivitis sicca was diagnosed on the basis of a type A rose bengal staining or a type B staining associated with an abnormal result in Schirmer's test. A probable diagnosis of keratoconjunctivitis sicca was made in patients with grade B rose bengal staining. Xerostomia was studied by salivary scintigraphy with a scintillation camera (Picker Dyna 4) after the intravenous injection of 148 MBq of sodium pertechnetate labelled with technetium-99m, with images obtained at 5, 10, 15, 20, 30, 45, and 60 minutes. Salivary flow was assessed following the criteria of Schall *et al*,[9] and degrees III and IV were considered as abnormal. A labial salivary gland biopsy sample was also obtained in each patient by puncture of the lower lip. The changes observed in 4 mm^2 of salivary gland were evaluated according to Chisholm and Mason,[10] with degrees III and IV being defined as pathological. Xerostomia was diagnosed when a degree IV labial biopsy sample and a degree III or IV salivary scintigraphy sample were obtained. A probable diagnosis of xerostomia was made in patients with a grade III labial biopsy sample, or grade IV scintigraphy alone.

A diagnosis of definite Sjögren's syndrome was made when two of the following features were present: keratoconjunctivitis sicca, xerostomia, and autoimmune disease. A probable diagnosis of Sjögren's syndrome was made: (*a*) when probable keratoconjunctivitis sicca was associated with probable xerostomia, or (*b*)

when an autoimmune disease was associated with probable keratoconjunctivitis sicca or xerostomia.

A control group was available for each diagnostic method. Rose bengal staining and Schirmer's test were performed on 30 subjects attending an ophthalmologic outpatient clinic for sight correction. The rose bengal test was normal in all control subjects, and a positive Schirmer's test was found in three subjects. Salivary scintigraphy was carried out in 20 patients admitted to the hospital for various illnesses excluding autoimmune and liver diseases. All had normal salivary flow rates. Lower lip samples were obtained at necropsy from 20 consecutive patients who died with no evidence of autoimmune disease. No histological abnormalities were found in the minor salivary glands. The age and sex distribution of controls was similar to that of the patients.

We used two gold standards for the evaluation of the diagnostic methods: (*a*) diagnosis of Sjögren's syndrome (based on the aforementioned concepts of defined, probable or absent); and (*b*) a lip biopsy sample (degrees III and IV being accepted as pathological).

STATISTICAL ANALYSIS

Sensitivity, specificity, positive predictive value (+PV) and negative predictive value (−PV) were assessed for each diagnostic method.[11] The level of statistical significance was established at 5% for all tests. Bayes's theorem was used to calculate the probability of disease according to the results of the diagnostic tests.[12]

Results

Ten per cent of the control subjects had a positive Schirmer's test. Thirty seven of the 142 patients had a positive rose bengal test in addition to a positive Schirmer's test. Therefore the latter was considered unnecessary as a diagnostic approach in our study. In this way, our exploratory workup starts with the rose bengal test, followed by salivary scintigraphy, with a lip biopsy sample being taken last. Definite keratoconjunctivitis sicca was present in 34 patients (24%) and xerostomia in 56 (39%). Keratoconjunctivitis sicca and xerostomia were present together in 28 patients (20%). Sixty two of the 142 patients (44%) had definite Sjögren's syndrome, twenty four (17%) had probable Sjögren's syndrome, and in the remaining 56 (39%) the diagnosis was ruled out (table 1).

The probability of the rose bengal test being negative in patients without Sjögren's syndrome is high (specificity 98%), but this technique can be either positive or negative in patients with Sjögren's syndrome (sensitivity 55%) (table 1). Although rose bengal positive patients have a strong likelihood of being affected by Sjögren's syndrome (+PV 92%), those who are rose bengal negative may or may not have Sjögren's syndrome (−PV 52%). Calculation of predictive values was carried out conservatively with the 24 patients (17%) labelled as 'probable SS' being excluded.

Rose bengal tests show another clinically remarkable feature: the technique divides patients into two groups, one (rose bengal positive) with a high occurrence of Sjögren's syndrome (92%) and the other (rose bengal negative) with a low occurrence of Sjögren's syndrome (27%) (table 1); these results are significantly different ($p<0{\cdot}0001$) from the initial 44% occurrence of Sjögren's syndrome. In the rose bengal positive group only two of 37 patients (5%) had 'probable Sjögren's syndrome', *v* 21% of patients in the rose bengal negative group.

In a rose bengal positive patient a positive salivary scintigraphy result has a 100% predictive value, thus making it unnecessary to obtain a labial biopsy sample. Conversely, a rose bengal positive patient with a negative salivary scintigraphy result indicates a likely false negative (−PV 7%) result (table 2).

In patients with positive rose bengal staining and positive salivary scintigraphy a lip biopsy

Table 1 Results of the rose bengal test

Patient group	*SS+*	*SS−*	*SSp*	*Total*
Patients with positive rose bengal staining	34	1	2	37
Patients with negative rose bengal staining	28	55	22	105
Total no of patients	62	56	24	142

(SS+) definite Sjögren's syndrome; (SS−) no Sjögren's syndrome; and (SSp) probable Sjögren's syndrome.
Prevalence SS+=62/142=44%; prevalence SSp=24/142=17%; specificity=55/56=98%; sensitivity=34/62=55%; positive predictive value=34/37=92%; and negative predictive value=55/105=52%.

Table 2 Results of salivary scintigraphy with positive rose bengal test

Patient group	*SS+*	*SS−*	*SSp*	*Total*
Patients with positive scintigraphy	22	0	0	22
Patients with negative scintigraphy	11	1	2	14
Not assessable	1	0	0	1
Total no of patients	34	1	2	37

Abbreviations as in table 1.
Prevalence SS+=34/37=91%; prevalence SSp=2/37=5%; not assessable=1/37=2·7%; specificity=1/1=100%; sensitivity=22/34=65%; positive predictive value=22/22=100%; and negative predictive value=1/14=7%.

Table 3 Results of salivary scintigraphy when rose bengal test was negative

Patient group	*SS+*	*SS−*	*SSp*	*Total*
Patients with positive scintigraphy	10	1	7	18
Patients with negative scintigraphy	16	53	15	84
Not assessable	2	1	0	3
Total no of patients	28	55	22	105

Abbreviations as in table 1.
Prevalence SS+=28/105=27%; prevalence SSp=22/105=21%; not assessable=3/105=3%; specificity=53/55=96%; sensitivity=10/28 =36%; positive predictive value=10/18=56%; and negative predictive value=53/84=63%.

sample showed 91% sensitivity and 100% +PV. In patients with positive rose bengal staining and negative salivary scintigraphy, a labial biopsy sample showed 100% specificity and 73% sensitivity. The +PV was 89% and the −PV 50%. Therefore, a labial biopsy sample may be useful in the rose bengal staining positive, salivary scintigraphy negative group of patients as a positive result will notably increase the diagnostic certainty.

Table 3 analyses negative rose bengal staining patients. Salivary scintigraphy is likely to be negative in patients without Sjögren's syndrome (specificity 96%); it can be positive or negative in patients with Sjögren's syndrome (sensitivity 36%). Nevertheless, the fact that 22 patients (21%) were labelled as 'probable Sjögren's syndrome' implies that the predictive value of salivary scintigraphy, given its high specificity, is not as useful as might be expected. Therefore, regardless of the salivary scintigraphy results, a given patient may or may not have Sjögren's syndrome (+PV 55%, −PV 63%); this implies that the usefulness of salivary scintigraphy is limited when a negative rose bengal staining result has been obtained.

In patients with negative rose bengal staining, the sensitivity and specificity of a labial biopsy sample are greater than 90% and unrelated to the salivary scintigraphy results. Although over one third of positive salivary scintigraphy patients have probable Sjögren's syndrome, this proportion is only 18% in negative salivary scintigraphy patients. The labial biopsy sample +PV was 69% in the negative rose bengal staining, positive salivary scintigraphy group; it was 48% when rose bengal staining and salivary scintigraphy were both negative. The labial biopsy sample −PV was 25% in negative rose bengal staining, positive salivary scintigraphy patients, and 94% in the negative rose bengal staining, negative salivary scintigraphy group.

The approach yielded seven diagnostic situations depending on the results of the three diagnostic steps. The analysis of the seven situations confirms that the expected negative correlation between the −PV and definite occurrence of Sjögren's syndrome was actually observed ($r=-0{\cdot}87$, $p=0{\cdot}01$). A positive correlation was also found between +PV and positive Sjögren's syndrome occurrence ($r=0{\cdot}89$, $p<0{\cdot}01$). There was a negative correlation between the +PV and probable Sjögren's syndrome occurrence ($r=-0{\cdot}60$, $p=0{\cdot}07$). Specificity correlates positively with Sjögren's syndrome occurrence ($r=0{\cdot}93$, $p<0{\cdot}01$) and, as expected, with +PV ($r=0{\cdot}79$, $p=0{\cdot}03$), and with −PV ($r=-0{\cdot}89$, $p<0{\cdot}01$).

The differences between the diagnosis of Sjögren's syndrome being regarded as the gold standard instead of a labial biopsy sample were not significant. These differences were noteworthy only when salivary scintigraphy was performed after a positive rose bengal staining result; in such instance the specificity decreased from 100% (Sjögren's syndrome as gold standard) to 67% (labial biopsy sample as gold standard). When the rose bengal staining was negative, the +PV of scintigraphy increased from 55 to 78%.

When Bayes's theorem is used, the probability of the disease being present if the rose bengal staining is negative and the salivary scintigraphy and lip biopsy sample are positive becomes 94%. When both rose bengal staining and salivary scintigraphy are positive, and the lip biopsy sample negative, the probability of disease is 39%. The probability of the disease being present if the three methods show positive results is 99·9%.

Discussion

Diagnostic techniques in Sjögren's syndrome are relatively simple. General agreement on the results yielded by the different methods is, however, lacking, and unified criteria for the diagnosis of Sjögren's syndrome need to be established.

During the first symposium on Sjögren's syndrome held in Copenhagen in 1986, Fox *et al* proposed the following criteria for the classification of this syndrome: Schirmer's test less than 10 mm and Van Bigsterveld's rose bengal classification for the diagnosis of keratoconjunctivitis sicca.[13] Non-stimulated sialometry ($\leq 1{\cdot}5$ ml/15 min), salivary scintigraphy, and a lip biopsy sample were used for the diagnosis of xerostomia. The presence of more than one focus of lymphoplasmocytary infiltration was proposed for the diagnosis of xerostomia. Similar criteria have been proposed by groups from Greece,[14] Japan,[15] Denmark,[16] and Italy.[17]

We propose a stepwise diagnostic approach. Sixty two patients with definite Sjögren's syndrome, 24 with probable Sjögren's syndrome, and 56 in whom Sjögren's syndrome was finally ruled out were studied. A lip biopsy appeared to be the best test for establishing the diagnosis. Other workers have reached the same conclusion.[18 19] Considering the wide range of salivary gland implication (probably related to the evolutionary stage of the disease), it appears advisable to devise a scale of histological damage. Several lip biopsy classifications have been proposed.[20 21] In our study, Chisholm's stage IV, and stage III associated with other positive diagnostic results, were considered to be pathological.

Scintigraphy and lip biopsy are easy to perform and may be useful in the diagnostic

approach to patients with ill defined clinical presentations. If xerostomia is shown, the doctor should search for an underlying autoimmune disease once other known causes of xerostomia have been ruled out.

In our study, Schirmer's test and the rose bengal test correlated positively, as did the rose bengal test with a positive lip biopsy sample. The rose bengal test was the best method for diagnosing keratoconjunctivitis sicca, and the lip biopsy sample the best for xerostomia. The latter was the method with the highest specificity, sensitivity, positive predictive value, and negative predictive value. Salivary scintigraphy and the rose bengal test were highly specific, but had low sensitivity.

Patients with a negative rose bengal test present a particular problem, as the other two tests (scintigraphy and lip biopsy) may not provide a definite diagnosis. Thus, rather than performing these two tests, it may be advisable to repeat the rose bengal test a few months later, and to withhold scintigraphy and the biopsy while the rose bengal test remains negative.

In patients with a positive rose bengal test, a positive salivary scintigraphy will confirm the disease. The lip biopsy sample seems redundant in rose bengal staining and salivary scintigraphy positive patients given that: (*a*) it will not be conclusive in 9% of patients; and (*b*) it will not add diagnostic certainty. If the salivary scintigraphy result is negative but rose bengal staining positive, a labial biopsy sample should be obtained.

We found 13 patients with a positive labial biopsy sample after rose bengal staining and salivary scintigraphy had proved negative. All had stage III histological damage. This group of patients should be included in a carefully planned follow up protocol as they may later develop definite Sjögren's syndrome.

Our results would have been more conclusive if patients with probable Sjögren's syndrome had been excluded. Such an exclusion, however, would be a methodological error leading to an overestimation of the performance of the diagnostic test.[11 22] From a clinical point of view, we consider it important that this group of patients is taken into account, particularly with respect to their follow up. As a result of this work we suggest that patients with 'probable' Sjögren's syndrome are considered a patient group with clinical and exploratory findings strongly suggestive of the disease, and that this group should be followed up and reassessed within one to two years.

This study indicates that the diagnosis of Sjögren's syndrome can be established through a sequence of tests performed in a stepwise manner. We propose rose bengal staining as the first test. Schirmer's test can be obviated owing to its low sensitivity and good correlation with rose bengal staining. If the latter is positive, xerostomia is always present. On the other hand, when rose bengal staining is negative, salivary scintigraphy should be performed. A positive salivary scintigraphy result is associated with a positive lip biopsy sample. A labial biopsy sample should be obtained when the salivary scintigraphy result is negative. Our results show that only 29 biopsy samples were needed to achieve a diagnosis of Sjögren's syndrome in 142 patients (20%). Hence the outlined approach may make it unnecessary to obtain biopsy samples in approximately 80% of patients with suspected Sjögren's syndrome.

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