CLINICAL PRACTICE
OPHTHALMOLOGICAL EXAMINATIONS OF PATIENTS WITH
PRIMARY SJÖGREN'S SYNDROME SELECTED FROM A
RHEUMATOLOGICAL PRACTICE

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SUMMARY

Ophthalmological examination of patients with primary Sjögren's syndrome (SS) ($n=44$) taken randomly from a rheumatological practice revealed that in this population group the eyes were frequently but not seriously involved ($n=42$). Primary SS patients ($n=44$) could not be separated from patients suspected of primary SS, in whom the diagnosis had been excluded ($n=21$) on the basis of ocular examination, but they were clearly distinguishable from healthy controls ($n=26$). The diagnostic value of the tests currently in use to establish the diagnosis keratoconjunctivitis sicca in primary SS such as Schirmer's, tear film break up time and rose bengal staining tests appeared to be limited. These results demonstrate the heterogeneity of the syndrome, the influence of patient selection on patient characteristics in different primary SS populations and the limited value of using the present classification criteria for the diagnosis primary SS in individual patients.

KEY WORDS: Keratoconjunctivitis sicca, Xerostomia, Multisystem autoimmune disease, Diagnosis, Primary Sjögren's syndrome.

PRIMARY Sjögren's syndrome (SS) is a multisystem autoimmune disease characterized by lymphocytic involvement of exocrine glands [1, 2]. Keratoconjunctivitis sicca (KCS) due to aqueous deficiency of the tear film and xerostomia or dry mouth are considered to be the dominating features, but patients may present with extraglandular symptoms such as articular manifestations [2-4]. Consequently, patients suspected of having primary SS are primarily evaluated by different specialists such as ophthalmologists, odontologists and rheumatologists. No international agreement has been reached on diagnostic criteria for primary SS and the application of diverse criteria may lead to a heterogeneous group of patients with a diagnosis of primary SS [5].

The most commonly used test-set to establish the diagnosis KCS includes an evaluation of tear quantity (Schirmer's test), tear quality (tear film break-up time) and ocular surface condition (rose bengal staining). To the best of our knowledge no studies have focused on the ocular abnormalities and the significance of the diagnostic tests for the presence of KCS in patients with primary SS who were referred to the rheumatologist.

The purpose of this study was: (1) to evaluate the ophthalmological abnormalities in primary SS patients who had been primarily referred to the Department of Rheumatology with complaints concerning joints and or muscles; and (2) to determine the diagnostic value of different tests currently in use for the evaluation of the ocular component of the syndrome. For this last purpose the ocular test results of primary SS patients were compared with those of patients attending the rheumatology outpatient clinic suspected of having primary SS and in whom the diagnosis had been excluded.

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PATIENTS AND METHODS

Patients

All patients with primary SS attending the outpatient clinic of the Department of Rheumatology of the Dr Daniël Den Hoed Clinic, Rotterdam were asked to participate in the study. Three patients refused and in the remaining 44 patients the diagnosis primary SS was based on the presence of all of the following modified Californian criteria for primary SS [6]: (1) complaints of oral and/or ocular dryness; (2) arthralgias and/or myalgias; (3) more than one focus of ≥ 50 mononuclear cells per 4 mm^2 salivary gland tissue from the lower lip [7] and/or abnormal parotid sialography according to the criteria of Rubin [8]; and (4) the presence of at least one of the following serological abnormalities: antinuclear antibodies (ANAs), rheumatoid factors (RFs) or antibodies to SS-A or SS-B antigens. Forty women and four men with primary SS aged 32-80 years (mean 55 years) with a disease duration of 1-30 years (mean 9 years) were studied. The main characteristics of the patients are listed in Table I.

Two groups of persons from the same outpatient department volunteered for the ophthalmological examinations and served as controls. The first group consisted of 21 patients (19 women, two men) suspected of having primary SS aged 31-72 years (mean 47 years) in whom the diagnosis had been excluded (NON-SS). These patients had been evaluated for the presence of primary SS because of joint and/or muscle complaints, a history of dryness of the eyes and/or the mouth and/or an abnormal Schirmer's test ($< 10 \text{ mm}$ in 5 min of both eyes). Exclusion of the diagnosis primary SS was based on the absence of parotid sialographic changes compatible with primary SS [8], a score grade 3 or less on the Chisholm scale [7] for minor salivary gland histology, and the absence of RFs, ANAs and anti SS-A and SS-B antibodies. The second group con-

TABLE I
CHARACTERISTICS OF 44 PATIENTS WITH PRIMARY SS

Characteristics	No. tested	No. positive	% Positive
Antinuclear antibodies	44	41	93
Anti SS-A antibodies	44	31	70
Anti SS-B antibodies	44	16	36
Rheumatoid factors	38	23	61
Parotid gland sialography	43	31	72
Minor salivary gland histology	39	34	87

sisted of 26 sex- and age-matched subjects who were recruited from the hospital staff and from patients attending for treatment of soft tissue rheumatic disorders without complaints of dryness of the eyes or mouth. None of the participants fulfilled the established criteria for another connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis.

Methods

All participants were requested to stop the use of artificial tear solutions at least 12 h prior to the investigation. They were questioned about the use of artificial tears and the presence of the following eye complaints: burning, foreign body sensation, itching, inability to tear and photophobia. The eyelids, the conjunctiva, the pupil reactions, the corneal tear film and the tear meniscus height were examined with a Haag Streit 900 slit lamp. Schirmer's test was performed without anaesthesia. The wetting of the standardized paper strip (IOLAB Pharmaceuticals, California) after 5 min was averaged for the two eyes. Next the tear film break-up time (BUT) was measured after touching the lower palpebral conjunctiva with a fluorescein strip moistened with one drop of saline. Participants were instructed to blink several times; the tear film was inspected with the standard cobalt blue filtered light of the slit lamp. The time between the last blink and the first appearance of a randomly appearing dry spot was measured with a stop watch. The BUT was measured three times, the mean of each eye was calculated and

the score was averaged for the two eyes. The Cochet-Bonnet aesthesiometer was used to determine the central corneal sensitivity and 55 mm or more nylon thread length was considered to be normal [9]. Next the eyes were anaesthetized with oxybuprocaine HCl 0.4% and applanation tonometry was performed with the Goldman tonometer. Thereafter 10 µl of 1% rose bengal (RB) solution was applied with a pipette. After 2–3 min waiting, the degree of staining of the nasal and the temporal conjunctiva and the cornea exposed between the interpalpebral fissures when looking straight ahead was estimated. Each area was given a score of 0–3, so that the maximum score for each eye was 9. The score was averaged for the two eyes. Both eyes were examined by direct and indirect ophthalmoscopy of the fundus in mydriasis.

All eye examinations were done in the same sequence, in the same room, within a period of 6 weeks and by one ophthalmologist (MH), who was unaware of the clinical diagnosis. The primary SS patients and the NON-SS patients underwent the complete ophthalmological examination; in the control subjects only Schirmer's test, BUT and RB staining were performed.

Statistics

Chi-square test with Yates' correction and Kendall's rank correlation test were used.

RESULTS

Thirty-nine primary SS (89%) and 17 NON-SS patients (81%) (difference not significant) had complaints of dryness of the eyes and artificial tears were regularly used by 32 primary SS patients (73%) and 10 NON-SS patients (48%) (NS). The symptoms and signs of all primary SS and NON-SS patients suggesting the presence of KCS are specified in Table II. One primary SS patient had severe dry eyes with a persistent epithelial defect and she was the only patient who had previously undergone a punctal occlusion. One other patient had mucous secretion at slit lamp examination and two patients suffered from a slight blepharitis. In none of the primary SS patients were pupil abnormalities found.

TABLE II
SYMPTOMS AND RESULTS OF EXAMINATION AT THE SLIT LAMP (WITHOUT STAINING) OF THE EYES OF PATIENTS WITH PRIMARY SS AND PATIENTS SUSPECTED OF PRIMARY SS IN WHICH THE DIAGNOSIS HAD BEEN EXCLUDED (NON-SS)

	Primary SS (n=44)			NON-SS (n=21)		
	No. positive	No. tested	%	No. positive	No. tested	%
Symptoms						
Foreign body sensation	30	44	68	12	21	57
Burning	30	44	68	13	21	62
Inability to tear	28	44	67	6	21	29
Itching	17	44	39	11	21	52
Photophobia	13	44	30	3	21	14
Signs						
Scanty tear meniscus	22	39	56	5	21	24
Cellular debris in precorneal tear film	22	39	56	0	21	0
Conjunctival redness	8	39	21	0	21	0
Keratitis punctata and/or filamentosa	6	39	15	0	21	0

TABLE III

NUMBER AND PERCENTAGE OF POSITIVE TEST RESULTS OF SCHIRMER'S TEST, BUT AND RB STAINING OF 44 PATIENTS WITH PRIMARY SS (1°SS), 21 PATIENTS SUSPECTED OF HAVING PRIMARY SS IN WHOM THE DIAGNOSIS HAD BEEN EXCLUDED (NON-SS) AND 26 CONTROL SUBJECTS (CONTROLS)

Diagnosis	Schirmer <12 mm	Schirmer <10 mm	Schirmer <8 mm	Schirmer <6 mm
1° SS	35/44 = 80%	34/44 = 77%	30/44 = 70%	27/44 = 61%
NON-SS	13/21 = 62%	12/21 = 57%	9/21 = 43%	6/21 = 29%
Controls	5/26 = 19%	4/26 = 15%	4/26 = 15%	3/26 = 12%
	BUT <12 s	BUT <10 s	BUT <8 s	BUT <6 s
1° SS	38/44 = 86%	38/44 = 86%	35/44 = 80%	31/44 = 70%
NON-SS	7/21 = 33%	6/21 = 29%	4/21 = 19%	1/21 = 5%
Controls	7/26 = 27%	7/26 = 28%	4/26 = 15%	1/26 = 4%
	RB staining ≥1	RB staining ≥2	RB staining ≥3	RB staining ≥4
1° SS	40/44 = 91%	35/44 = 80%	29/44 = 66%	20/44 = 45%
NON-SS	9/21 = 43%	6/21 = 29%	4/21 = 19%	0 = 0%
Controls	11/26 = 42%	4/26 = 15%	1/26 = 4%	0 = 0%

For each test results of different cut-off levels are shown.

Table III shows the frequency of positive test results of Schirmer's test, BUT and RB staining with respective cut-off points in all participants. Low cut-off levels for Schirmer's test and BUT resulted in low values of sensitivity and high values of specificity (specificity = 100% — percentage false positive). Applying a cut-off value of 8 s the sensitivity and specificity of BUT were 80% and 81% respectively. RB staining was highly specific (100%) but not sensitive (45%) when a score ≥4 was used as cut-off value; at lower cut-off levels the sensitivity rose at the expense of a low specificity. A RB staining score ≥1 yielded the highest sensitivity (91%). The sensitivity and specificity determined from NON-SS patients of two out of three tests positive, i.e. Schirmer's test <10 mm in 5 min BUT <10 s and RB staining ≥ score 4 were 80% and 76% respectively. Sensitivity and specificity of at least one test positive was 96% and 59% respectively. When the cut-off values of the different tests were varied, no significant better diagnostic combination was found (data not shown).

In all participants Schirmer's test showed a positive correlation with BUT ($P < 0.01$), a negative correlation with RB staining ($P < 0.01$) and BUT correlated negative with RB staining ($P < 0.01$). In relation to the age of all participants both Schirmer's test ($P < 0.01$) and BUT ($P < 0.01$) showed a negative correlation and no correlation between age and RB staining was found. In the patients with primary SS no correlation between the disease duration and Schirmer's tests or BUT was found. RB staining correlated positive with the disease duration ($P < 0.05$). Intra-ocular pressure and fundoscopy were normal in all primary SS and NON-SS patients. In 12 out of 31 (39%) patients with primary SS and four out of 19 (21%) NON-SS patients (NS) a lowered corneal sensibility was found. The nylon thread lengths of the primary SS patients (mean 54.1 mm, standard deviation 1.7) did not differ from those of the NON-SS patients (mean 55 mm, SD 2.5).

DISCUSSION

Primary SS is a heterogeneous disease. Patients may present with many different manifestations and no international agreement on diagnostic criteria exists.

Consequently varying referral patterns and diagnostic criteria used may lead to different clinical characteristics of populations of patient with primary SS from different centres [5]. In this study only patients from one rheumatological outpatient clinic referred for muscle and/or joint complaints who fulfilled strictly defined criteria were included. The patients in this study were defined without using tests to establish the ocular component of the syndrome, but their clinical characteristics were similar compared to previous series of patients with primary SS in which KCS was used as an inclusion criterion (Table I) [7, 10–12].

Our data indicate that the ophthalmological manifestations in this population of patients with primary SS are rather mild. Five primary SS patients (11%) had no complaints of dry eyes at all. Primary SS patients had the same complaints of dry eyes as the NON-SS patients, which means that in a rheumatological practice subjective criteria for KCS are rather useless for differentiating the patient groups.

In the primary SS patients only one patient exhibited a corneal defect and mild injection of the conjunctiva or signs of keratitis were found in 21% and 15% respectively. These observations are in contrast with previous studies from ophthalmology clinics in which slit-lamp examination demonstrated conjunctival infiltration and injection in 70% of the patients with primary SS and recurrent bacterial keratitis and sterile corneal stromal melting in 25% of patients [13, 14]. These contradictory results may be due to patient selection.

The central corneal sensibility of the primary SS patients was similar compared to the NON-SS patients. In contrast to other investigators, we do not think this test has diagnostic value in primary SS [15, 16].

The diagnosis KCS in primary SS is usually established by the presence of two out of three positive tests including Schirmer's test (<10 mm in 5 min), BUT (<10 s) and RB staining (>3.5 Van Bijsterveld score), though other tests including tear fluid osmolality and tear fluid concentration of lysozyme, lactoferrin and IgA and conjunctival impression cytology are advocated [5, 15–17]. In this study the patients were categorized as primary SS from a rheumatological point of

view. Although this is in contrast to most previous studies in which patients with well defined KCS were used as the gold standard and extra-ocular features were not included, the sensitivity of Schirmer's test, BUT and RB staining found in the primary SS patients were similar [17–20].

Schirmer's test is frequently used as a first screening procedure in patients suspected of having primary SS. Previous studies using cut-off values from 19 to 3 mm demonstrated a sensitivity of 97% to 100% and a specificity (determined from healthy control subjects) of 32% to 100% respectively [17–20]. In this study the values for sensitivity applying cut-off values of 12 mm to 6 mm varied from 80% to 61% and the specificity determined from control subjects varied from 81% to 88% (Table III). However, comparing the primary SS and the NON-SS patients the values for specificity varied between 38% and 71%. These low values could be expected, since an abnormal Schirmer's test had been used as one of the inclusion criteria for the NON-SS patient group. This does not alter the fact that in the rheumatological practice Schirmer's test does not seem to be a very valuable screening test in patients with complaints of ocular and/or oral dryness, since it did not differentiate patients with and without primary SS. In agreement with previous studies we found a slightly positive RB staining to be very sensitive but not very specific and the reverse counts for a strongly positive test result. The high sensitivity of a RB staining score ≥ 1 , the independency of age and the positive correlation with disease duration signify that this test is the best one to rule out KCS. The BUT, using a cut-off value of 8 s, yielded the best results for both sensitivity and specificity.

Through the application of the currently used criteria for KCS in primary SS, i.e. Schirmer's test (<10 mm in 5 min), BUT (<10 s) and RB staining (>3.5 Van Bijsterveld score), we found a prevalence of KCS (two of three tests positive) in 80% of the patients. In 42 out of 44 primary SS patients (96%) at least one test was positive. The nine patients not fulfilling at least two positive ocular criteria pose a problem of taxonomy since all currently used classification criteria for primary SS consider the presence of KCS as a key symptom for the diagnosis of definite primary SS [5]. Considering the strict inclusion criteria used in this study and the similarity of the clinical characteristics of the patients studied (Table I) compared to those of other studies [7, 10–12] we feel that these results illustrate the wide clinical spectrum of the syndrome, the heterogeneity among patients from different centres and the fact that the cut-off values of the different tests are disputable.

In conclusion, our data demonstrate that in patients with primary SS who were selected from a rheumatological practice, manifestations of KCS are common. However, no indication was found that in this patient population involvement of the eyes was clinically and functionally very significant, which is in contrast to patients selected from the ophthalmological practice. The absence of symptoms and/or signs of KCS does not

exclude the presence of primary SS. From the tests currently used to confirm the presence of KCS in primary SS presenting with joint and/or muscle complaints, the BUT seems to be the best test, Schirmer's test is both unsensitive and unspecific and RB staining may be used for its high sensitivity at low scores and its high specificity at high scores.

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