Prevalence of Sjögren’s syndrome in ambulatory patients according to the American–European Consensus Group criteria


Objective. To estimate the prevalence of Sjögren’s syndrome (SS) in ambulatory patients attending a tertiary care centre, according to the American–European Consensus Group criteria, using a structured approach.

Methods. Three hundred patients from rheumatology and internal medicine clinics were randomly chosen. During the screening phase, a face-to-face interview, a screening questionnaire, a Schirmer-I test and a wafer test were carried out in all patients. During the second phase, patients with positive screening had confirmatory tests including fluorescein staining test, non-stimulated whole salivary flow and autoantibody testing. Confirmatory tests were also done in 13 patients with negative screening. In the last phase, lip biopsy was proposed to those patients who met pre-established criteria.

Results. Females constituted 79% of the study population. The mean age of the subjects was 42.8 ± 15.7 yr. Two hundred and twenty patients (73%) had positive screening. Fifty-five (27%) out of 204 patients evaluated showed keratoconjunctivitis sicca and 28 (13%) out of 215 patients xerostomia. One hundred and sixty-eight patients met criteria for lip biopsy and it was performed in 80 subjects who accepted the procedure. Focal sialoadenitis was demonstrated in 39 patients (49%), but only 28 of them met criteria for SS. In total, 40 patients were classified as SS. The minimum prevalence of SS in the population studied was 13.3% (95% CI 9.5–17.1%). The structured approach used in this study allowed 24 (60%) undiagnosed cases of SS to be identified.

Conclusion. SS is common among ambulatory patients attending a tertiary care centre and in most of them it is undiagnosed.

KEY WORDS: Sjögren’s syndrome, Screening, Prevalence.

Sjögren’s syndrome (SS) refers to keratoconjunctivitis sicca (KCS) and xerostomia (XT) resulting from immune lymphocytes that infiltrate the lacrimal and salivary glands [1]. Although SS has been considered to be the most common connective tissue disease, epidemiological data are scarce. The US National Arthritis Data Workgroup, the single source of national data on the prevalence and socioeconomic impact of the rheumatic disorders, did not include SS either in their 1989 report [2] or in its updated version in 1998 [3]. A book on the epidemiology of rheumatic diseases does not include SS either [4]. Perhaps 1–2 million individuals in the United States, most undiagnosed, are affected [5].

The prevalence of SS reported in two population studies conducted in Greece was 3.6 and 4.8% respectively [6, 7]. In a population-based survey conducted in Manchester, UK, SS was diagnosed in 3–4% of subjects aged 18–75 yr [8]. Epidemiological studies on the prevalence of SS are limited in part because of the heterogeneity of the populations studied, the use of different diagnostic tests for the evaluation of lacrimal and salivary gland involvement and the use of different classification criteria for the disease. In addition, since the disease may have an insidious onset, a variable course and a wide spectrum of clinical manifestations [6, 7, 9–12] patients with SS may be missed or misclassified [10, 13], or the diagnosis may be delayed.

Several sets of classification criteria for SS have been proposed [14–18]. Recently, the American–European Consensus Group (AECG) published a revised version of the European criteria. The authors consider the modified criteria set to be probably the best possible instrument currently available for the classification of patients with SS [19].

In this study, we aimed to estimate the prevalence of SS in ambulatory patients attending a tertiary care centre according to the AECG criteria [19], using a structured approach.

Patients and methods

Three hundred and thirty-six patients were selected using random numbers from the rheumatology and internal medicine clinics. Thirty-six declined to participate, therefore 300 were included in the study (recruitment fraction 89%). Subjects who had taken any medication that may reduce salivary flow (i.e. antihistamines) within 48 h before the study...
were excluded. All participants were asked to refrain from eating, drinking, smoking, chewing or oral hygiene procedures for at least 1 h 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 three phases: screening, confirmatory tests and lip biopsy.

During the screening phase of the study, all patients had a face-to-face interview with a single physician, blinded to medical diagnoses, using a standardized form which included questions about demographic data, health-related behaviours and use of medications. In addition, a validated screening questionnaire for sicca syndrome [14, 20], the Schirmer-I test [21] and the wafer test [20] 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 positive screening.

In the second phase of the study, patients with positive screening underwent confirmatory tests including the fluorescein staining test, non-stimulated whole salivary flow rate (NSWSF) and autoantibodies. Confirmatory tests were also done in a random sample of 13 patients with negative screening.

During the last phase of the study, lip biopsy was proposed to all patients who had ≥2 of the following results: (1) at least one affirmative answer to the oral component of the screening questionnaire, (2) wafer test >4 min, (3) presence of keratitis by the fluorescein staining test, (4) NSWSF <0.3 ml/min, (5) positive anti-Ro and/or anti-La antibodies.

Setting

The Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán is one of the Institutes of Health in Mexico. It is a tertiary care centre 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 yr, 85.5% females); 4813 (81.0%) have connective tissue disease diagnoses. The internal medicine clinic provides regular care to 10 314 patients (70.0% females).

Definitions

The following definitions are used in the study:
- EQ5 refers to one or more affirmative answers to the questionnaire.
- Dry eye symptoms refer to one or more affirmative answers to the ocular component of the questionnaire.
- Xerophthalmia refers to a Schirmer-I test ≤5 mm in 5 min.
- Dry mouth symptoms refer to one or more affirmative answers to the oral component of the questionnaire.
- XT refers to salivary flow rate ≤0.1 ml/min [9].
- Dry eye and dry mouth symptoms refer to one or more affirmative answers to the ocular and oral component of the questionnaire.
- KCS was diagnosed with the fluorescein staining test [19].
- SS was defined according to the criteria proposed by the AECG [19].

Schirmer-I test

The Schirmer-I test was done as previously described [21], using two standardized sterile filter paper strips (Sno Strips, Chauvin Pharmaceuticals, Romford, Essex, 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 previously described [20]. In brief, the patient was asked to sit in a relaxed and upright position and not to speak during the test. After swallowing any residual saliva, the wafer was put on the centre of the subject’s tongue. The patient was asked to close the mouth and keep the wafer in the mouth without chewing or swallowing it, but swallowing saliva was allowed. Time of dissolution of the wafer, as measured from the moment when the wafer was put on the tongue until it had dissolved, was the main outcome. The test was considered as positive if the time of dissolution of the wafer was more than 4 min.

Eye evaluation

The condition of the corneal surface was evaluated by an ophthalmologist, using the fluorescein staining test. The ophthalmologist was unaware of the results of the screening procedure and the patient’s diagnosis.

Non-stimulated whole saliva flow (NSWSF) collection

NSWSF was measured by the spitting method [22]. In brief, with the subject seated comfortably, he or she was instructed to rest for 5 min before the test, minimize orofacial movements and not to speak. Before starting the procedure, but not later, the patient swallowed any residual saliva and was then asked to allow all saliva to accumulate on the floor of the mouth and to spit it into a graduated test tube every minute. Saliva was collected for a period of 5 min [22, 23] and the measured volume expressed in ml/min.

Autoantibodies

A blood sample was drawn and serum was stored at −70°C, for testing of the autoantibodies at the end of the second phase of the study. Rheumatoid factor was tested by nephelometry; anti-nuclear antibodies were tested by indirect immunofluorescence using Hep-2 cells as substrate; the serum antibodies to Ro/SSA and La/SSB were tested by enzyme-linked immunosorbent assay (ELISA).

Lip biopsy

Minor salivary glands were obtained through normal-appearing mucosa by an oral surgeon. Biopsy specimens contained two to 10 glands (median five); 90% of the specimens contained four to seven glands. The area of the gland tissue was measured with a 10 × 10 mm graticule at ×40 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 a number of lymphocytic foci containing more than 50 lymphocytes per 4 mm² of glandular tissue [19, 21, 24].

Statistical analysis

Descriptive statistics were used to define the subjects’ characteristics in each group. Categorical variables were compared using χ² or Fisher’s exact test. Continuous variables were analysed using Student’s t-test. Prevalence estimates are reported with 95% confidence interval. A P value was set at <0.05, two-tailed. Analysis was performed using the STATA 5.0 computer program (Stata Corporation, College Station, TX.).

The study was approved by the Institutional Committee of Biomedical Research and all patients signed an informed consent.
Results

Population characteristics

Three-hundred and thirty-six patients were selected using random numbers from the rheumatology (n=197) and internal medicine (n=139) clinics. Thirty-six declined to participate therefore 300 (rheumatology 181, internal medicine 119) were included in the study. Females constituted 79% of the total study population. The mean age of the subjects was 42.8±15.7 yr (range 16–83 yr) and the educational level 10.9±5.3 yr. Patients from rheumatology and internal medicine were comparable in terms of age and smoking. However, patients from rheumatology were more commonly females, had a higher educational level and a lower smoking index (Table 1).

Patients’ diagnoses in rheumatology were mostly connective tissue diseases (84%), and in internal medicine endocrine diseases, systemic arterial hypertension, obesity and peptic disorders (61%); only 15% of patients had a rheumatic disorder.

Screening

Two-hundred and twenty patients (73%) were positive to screening—rheumatology 140 (77%), internal medicine 80 (67%); P<0.052. The distribution of the results to the different tests was as follows: EQ1 146 (49%) patients, dry eye symptoms 118 (39%), dry mouth symptoms 103 (34%) and dry eye and dry mouth symptoms 74 (25%). Xerophthalmia was detected in at least one eye in 101 (34%) patients and in both eyes in 67 (22%). The wafer test was abnormal in 187 (62%) patients.

The proportion of patients with affirmative answers to the screening questionnaire and with xerophthalmia was significantly higher in rheumatology than in internal medicine, but the prevalence of XT was similar in both groups (Table 3).

Among the thirteen patients with negative screening in whom confirmatory tests were carried out, one patient had isolated KCS and another had isolated XT.

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the study population</th>
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<tr>
<td>Total population, n=300</td>
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<tr>
<td>Female, n (%)</td>
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<tr>
<td>Age, mean±S.D. (yr)</td>
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<td>Education, mean±S.D. (yr)</td>
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<td>Smoking ever, n (%)</td>
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<td>Smoking index*, mean±S.D.</td>
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*P value refers to the comparison between patients from rheumatology and internal medicine.

<table>
<thead>
<tr>
<th>TABLE 2. Results of the screening in the study population</th>
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<tr>
<td>Test</td>
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<tr>
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<tr>
<td>European Questionnairea (EQ1), n (%)</td>
</tr>
<tr>
<td>Dry eye symptomsa, n (%)</td>
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<td>Dry mouth symptomsa, n (%)</td>
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<td>Dry eye and dry mouth symptomsa, n (%)</td>
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<tr>
<td>Xerophthalmia (one eye)b, n (%)</td>
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<tr>
<td>Xerophthalmia (both eyes), n (%)</td>
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<td>Wafer test, n (%)</td>
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*P value refers to the comparison between patients from rheumatology and internal medicine.

Prevalence of keratoconjunctivitis sicca and xerostomia

Among the 220 patients with positive screening, confirmatory tests were carried out as follows: NSWSF 215, fluorescein staining test 204, antinuclear antibodies 215 and rheumatoid factor, anti-Ro/SSA and anti-La/SSB 216 patients. Fifty-five (27%) patients were diagnosed with KCS, 28 (13%) with XT and 39 (18%) tested positive to anti-Ro/SSA or anti-La/SSB antibodies. The proportion of patients with KCS was significantly higher in rheumatology than in internal medicine, but the prevalence of XT was similar in both groups (Table 3).

Among the thirteen patients with negative screening in whom confirmatory tests were carried out, one patient had isolated KCS and another had isolated XT.

Lip biopsy

One hundred and sixty-eight patients met criteria for lip biopsy. Eighty-eight patients rejected the procedure and in 80 (48%) the difference was seen between either group in the results to the wafer test (Table 2).

<table>
<thead>
<tr>
<th>TABLE 3. Results of confirmatory tests in the study population</th>
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<tr>
<td>Test</td>
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<tr>
<td>Keratoconjunctivitis sicca, n (%)</td>
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<tr>
<td>Xerostomia, n (%)</td>
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<tr>
<td>ANA, n (%)</td>
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<tr>
<td>RF, n (%)</td>
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<tr>
<td>Anti-SSA, n (%)</td>
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<td>Anti-SSB, n (%)</td>
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<tr>
<td>Anti-SSA or -SSB, n (%)</td>
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<td>Anti-SSA and -SSB, n (%)</td>
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*P value refers to the comparison between patients from rheumatology and internal medicine.

Concurrent tests were performed as follows (total population/rheumatology/internal medicine): fluorescein staining test (204/137/73), NSWSF (215/137/78), antinuclear antibodies (ANA) (215/137/78), rheumatoid factor (RF) (216/138/78), anti-Ro/SSA (216/138/78) and anti-La/SSB (216/140/76) patients.

Keratoconjunctivitis sicca as diagnosed with the fluorescein staining test.

Xerostomia refers to salivary flow rate ≤0.1 ml/min.

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<sup>a</sup>Confirmatory tests were performed as follows (total population/rheumatology/internal medicine): fluorescein staining test (204/137/73), NSWSF (215/137/78), antinuclear antibodies (ANA) (215/137/78), rheumatoid factor (RF) (216/138/78), anti-Ro/SSA (216/138/78) and anti-La/SSB (216/140/76) patients.

<sup>b</sup>Keratoconjunctivitis sicca as diagnosed with the fluorescein staining test.

<sup>c</sup>Xerostomia refers to salivary flow rate ≤0.1 ml/min.
biopsy was performed. In 39 (49%) patients lip biopsy showed focal sialoadenitis; however, only 28 patients fulfilled criteria for SS. One patient with systemic lupus erythematosus had no affirmative answers in the screening questionnaire, but she had a Schirmer-I test ≤ 5 mm, NSWSF ≤ 0.1 ml/min and focal sialoadenitis in lip biopsy. In strict adherence to criteria definition, although she did not meet criteria for secondary SS she did for primary SS; thus, we considered her a case.

**Prevalence of Sjögren’s syndrome**

In addition to the 28 patients with focal sialoadenitis who fulfilled SS criteria, 12 patients met criteria for SS despite lip biopsy not performed or not showing focal sialoadenitis; therefore 40 patients were classified as having SS (35 rheumatology and five internal medicine). According to these data, the minimum prevalence of SS syndrome in the total population was 13.3% [95% confidence interval (CI) 9.5–17.1] in rheumatology 19.3% (95% CI 13.6–25.0) and in internal medicine 4.2% (95% CI 0.7–7.7).

Eight patients in the total population were classified as primary SS (prevalence 2.7%, 95% CI 0.9–4.5), five in rheumatology (2.8%; 95% CI 0.4–5.2) and three in internal medicine (2.5%; 95% CI −0.3–5.3). Thirty-two patients in the total population were classified as secondary SS (prevalence 10.7%, 95% CI 7.2–14.2), 30 in rheumatology (16.6%, 95% CI 11.2–22.0) and two in internal medicine (1.7%, 95% CI −0.6–4.0) (Table 4).

Twenty-seven (9%) patients had been diagnosed as SS, on a clinical basis, by their treating physicians. In 16 the diagnosis was confirmed and in 11 it was ruled out with the current approach. The structured approach used in this study allowed 24 (60%) undiagnosed cases of SS to be identified.

**Discussion**

Using a structured approach in ambulatory patients attending a tertiary care centre, a minimum prevalence of SS of 13.3%, according to the AECG criteria [19], was detected. In order to increase the sensitivity and avoid missing any patient who might have SS, screening was carried out with three different instruments administered in parallel: the European questionnaire, which has been proposed for the selection of potential patients with sicca syndrome in epidemiological surveys [14]; the Schirmer-I test; and the wafer test, which has shown high accuracy in the classification of patients with normal and decreased salivary flow, has a good correlation with sialometry and has shown to be a strong predictor for XT [20]. The prevalence of dry eyes/mouth symptoms and xerophthalmia in our study is similar to that reported among 636 patients with rheumatoid arthritis from the Oslo Rheumatoid Arthritis Register [25], using a similar approach. No estimates exist for the wafer test. As expected, more patients from rheumatology screened positive than patients from internal medicine. Also, in a random sample of patients with negative screening none met the criteria for SS. Thus, we consider the screening process was adequate.

Confirmatory tests were carried out in all but one patient with positive screening. KCS was diagnosed with the fluorescein staining test [19] and XT was defined according to the NSWSF result. Saliva was collected by the spitting method for 5 min, which has been shown to be an adequate collection period, with the method being reproducible and reliable [22, 23]. Because salivary flow rates vary significantly among individuals, and in the same individual under different conditions, we standardized saliva collection for body position, time of the day, time since last major oral stimulus, exposure to light and olfactory stimuli. KCS was detected more commonly in patients from rheumatology than internal medicine; however, no significant difference was seen in the prevalence of XT between patients from either clinic. The prevalence of XT detected among the patients in internal medicine is similar to that reported in no SS disease controls from the European Community Study Group [12], and the estimate derived from the patients in rheumatology agrees with that found in the Oslo Rheumatoid Arthritis Register [25].

Lip biopsy was proposed to all patients who met the criteria for it, according to the results of the screening phase and the confirmatory tests. One hundred and sixty-eight patients met the criteria for lip biopsy, but it was performed only in the 80 who accepted the procedure. In 39 (49%) patients the result was compatible with SS; however, only 28 patients fulfilled criteria for SS. There were 11 patients with focal sialoadenitis in lip biopsy plus other items included in SS criteria list who they did not fulfill the criteria.

SS was defined according to the criteria proposed by the AECG [19]. According to these data, the minimum prevalence of SS in the population studied was 13.3%; however, this is a conservative estimate since we are considering that in those patients who rejected the biopsy, the result would be negative if the lip biopsy had been performed. Also, parotid sialography and salivary scintigraphy were not systematically requested.

Twenty-seven patients had been diagnosed as SS by their treating physicians, on a clinical basis. In 16 patients the diagnosis was confirmed and in 11 it was ruled out with the current approach. The structured approach used in this study allowed 24 undiagnosed cases of SS to be identified. These results reflect how frequently SS is missed even in tertiary care centres.

The study was conducted in a hospital where most patients are admitted or referred for specialized care, due to complex diseases. The participation rate in both clinics was high. The population selected from the rheumatology clinic was similar in age, gender and diagnoses to all the patients attending the clinic, thus we consider our results extrapolate to the whole population. Also, the population studied from the internal medicine clinic had a similar gender distribution to the whole population of patients followed in that clinic; unfortunately, since we do not have a detailed registry of the age and diagnoses from this clinic we cannot be certain about the generality of our results. Nevertheless, we have the sense that the population studied from this clinic is representative of all the patients. For these reasons, we consider that the figures obtained reflect the prevalence of SS in patients with chronic diseases.

Epidemiological data about SS are scarce. The US National Arthritis Data Workgroup did not include SS in either the 1989 report [2] or in its updated version in 1998 [3]. A book on the epidemiology of rheumatic diseases does not include SS [4]. Paradoxically, SS has been considered to be probably the most common connective tissue disease.

Few studies have assessed the prevalence of SS in the general population. In a study conducted in a Greek rural community, a diagnosis of definite primary SS was made in 0.6% (95% CI 0.19–1.39) of 837 women aged 18 years or older [6]. Among an
apparently healthy elderly population (age 67–95 yr), residents of a public nursing home in Greece, the prevalence of primary SS was 4.8% [7]. Although none of the subjects had anti-SSA or anti-SSB antibodies they had sicca symptoms and lip biopsy compatible with SS. In a population-based survey conducted in Manchester, UK, SS was diagnosed in 3.4% of adults aged 18–75 yr [8]. Diagnosis of SS was based on the original version of the European classification criteria [14]. When the presence of autoantibodies, the single objective criterion assessed, was mandatory for the classification of SS the prevalence was reduced to 1.76%. After adjusting for non-response and non-participation bias the estimate decreased to 0.8% (95% CI 0.3–1.6).

Although our estimate of primary SS is similar to the figures reported in the general population, comparison between our results and those from population surveys has been hampered by methodological heterogeneity, such as the use of differing classification criteria sets, differing ages of subjects studied and differing population and health status, among others. Estimating the prevalence of SS based on the original version of the European classification criteria for SS [14] may introduce some misclassification bias [19] resulting in overestimation.

It needs to be highlighted that our estimate of the prevalence of SS derives from patients who fulfilled the new set of criteria where at least one of the most specific markers for SS (focal sialoadenitis or anti-Ro/La antibodies) is mandatory, and reflects the minimum prevalence in a population of patients with chronic diseases. Since no other study has assessed the prevalence of SS using the AECG criteria, we cannot make a direct comparison of our results.

SS, like most connective tissue diseases, may have an insidious onset, variable course and a wide spectrum of clinical manifestations [6, 7, 9–12]. Due to the variability of the condition at disease presentation, patients may be missed or classified [10, 13] or the diagnosis be delayed. In a population-based study, patients identified as having primary SS had had mild complaints of dry eyes and mouth for several years, they were not aware of the disease and none of them had asked for medical care for their condition [6]. In clinical practice, only subjects with definite symptoms or in whom KCS has been diagnosed are investigated for SS [10, 13]; less often, patients with asymptomatic XT alone will be studied unless they are very symptomatic. Paradoxically, in subjects with sicca symptoms who later develop SS, oral symptoms are found more frequently than ocular symptoms at baseline [10]. As a result, the diagnosis of primary SS is made later than that of the secondary form [26] or is conditional on the presence of KCS [13]. This may explain why patients with secondary SS show abnormal results in the oral and ocular tests less frequently and less markedly than patients with primary SS [12]. The scarce information about SS at earlier stages and in patients with predominantly oral involvement [27] favours a biased and incomplete knowledge. Early recognition of patients with SS will be helpful in the understanding of the spectrum of the disease.

Several sets of classification criteria for SS have been proposed for patients with a complete spectrum of manifestations [14–18]; however, mild, early and atypical forms of the disease may be excluded, a limitation shared by the new set of criteria as shown by the eleven patients in this study with focal sialoadenitis in lip biopsy who were not classified as SS because they did not fulfill the criteria. As definite cases represent only a subset of the entire population of patients with a specific disease, the real prevalence of SS is most likely higher than the figures reported, including ours.

Some caveats about the study need to be considered. This is a single-centre study, thus the figure obtained reflects the prevalence of SS in the population attending our institute. The study was conducted among patients attending a tertiary care centre, therefore the prevalence of SS reported could be different from the prevalence among patients in primary care clinics. The prevalence of SS reported is most likely underestimated, since lip biopsy was not done in all patients and parotid sialography and salivary scintigraphy were not systematically requested.

Some strengths of the study should be considered. Patients were chosen using random numbers and were studied using a structured approach. We excluded patients in whom sicca symptoms might be due to medications. XT and KCS were diagnosed using strict criteria and SS was defined according to the most up to date version of the classification criteria, which probably represents the best possible instrument currently available for the classification of patients with this disease. Since we studied patients from two ambulatory clinics, the estimate derived from rheumatology would reflect the prevalence of SS expected in a high-risk population, while the estimate derived from the internal medicine population would reflect the expected figure in most medical services.

Based on these results, we may conclude that SS is common among ambulatory patients attending a tertiary care centre, and in most of them the diagnosis is missing. Following a structured approach favours its recognition.

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**Key messages**

- The prevalence of Sjögren’s syndrome among ambulatory patients from a tertiary care centre is 13.3%.
- The estimate varies: among patients attending rheumatology it is 19.3%, while in most medical services, i.e. internal medicine, it is 4.2%.

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