

CONCISE REPORT

Incidence of primary Sjögren's syndrome in Slovenia

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Objective: To determine the annual incidence of primary Sjögren's syndrome (pSS) in Slovenia.

Methods: All patients admitted to our department of rheumatology or referred to our outpatient clinic between 1 January 2000 and 31 December 2002 owing to sicca symptoms or because of a suspicion of SS were examined. Our rheumatological department is the only tertiary referral centre for the Ljubljana region, which has a population of 599 895 Caucasian people. All patients were evaluated by the validated European criteria for SS. The exact 95% confidence interval (CI) based on binomial distribution was created for the incidence estimate.

Results: 248 patients were examined; 71 of them (28.6%; 65 women, 6 men) were diagnosed as having pSS. Their mean (SD) age was 51.3 (14.5) years (range 19–78). The average annual incidence for pSS in our study population was calculated as 3.9 cases per 100 000 inhabitants (95% CI 1.1 to 10.2).

Conclusion: The estimated annual incidence of pSS in Slovenia is 3.9/100 000.

Ljubljana region, which has a Caucasian population of 599 895. All patients were evaluated using the validated European criteria for SS.⁸

Clinical assessment

After the first visit, all patients were asked to come to our department between 9 00 and 11 00 am, fasting and without brushing the teeth, mouth rinsing, or tobacco smoking for at least 1 hour before the examination. Six questions to assess both ocular and oral involvement were asked of each patient. Information on comorbidities, tobacco smoking, and related treatment was collected at the same time. Besides the questionnaire, all patients were subjected to a Schirmer-I test, unstimulated salivary flow test, rose bengal score determination, and serological tests. If necessary, salivary scintigraphy and histopathological investigation of the minor salivary glands were carried out until three of the six European classification criteria for SS were shown to be negative or until SS was diagnosed.

The ocular and oral tests were considered positive as follows: Schirmer-I test (wetting of ≤ 5 mm of the paper strip in 5 minutes (Alcon, USA)), unstimulated salivary flow test (≤ 1.5 ml of saliva collected in 15 minutes), rose bengal score ≥ 4 according to the van Bijsterveld scoring system.⁹

By salivary scintigraphy of the major salivary glands, 120 consecutive scans, 30 seconds each, were performed. Scans were assessed according to Schall's criteria.¹⁰

The histopathological examination of a minor salivary gland bioptic specimen was considered positive if the focus score was ≥ 1 (a focus defined as an agglomeration of at least 50 mononuclear cells; the focus score defined as the number of foci per 4 mm² of glandular tissue).⁹

Serological tests

The following serological tests were performed: antinuclear antibodies by indirect immunofluorescence on HEp-2 cell line substrate (Immuno Concepts, USA). A serum was considered antinuclear antibody positive when clearly discernible nuclear staining was seen at a serum dilution of at least 1:40. Anti-Ro/SSA and anti-La/SSB antibodies were tested by counterimmunoelectrophoresis.¹¹

Statistical analysis

The exact 95% confidence interval (CI) based on binomial distribution was created for the incidence estimate.

RESULTS

In the 3 year study period we examined 248 patients suspected of having pSS. Seventy one of them (28.6%; 65 women, 6 men) were diagnosed as having pSS. Their mean (SD) age was 51.3 (14.5) years (range 19–78). The average duration from the beginning of symptoms to diagnosis was 4.9 years (range 2 months to 15 years). Table 1 shows the data on the referring physicians and suspected diagnoses. As evident from the table, 127 (51.2%) patients were originally assumed to have SS (sicca complex as referral diagnosis), the second most common referral diagnosis was arthritis/

Primary Sjögren's syndrome (pSS) is characterised by symptoms of dry eyes and dry mouth. Exocrine tissues are the principal target sites, but many non-exocrine structures may be affected as well.¹ The disease primarily affects women during the fourth and fifth decade of life, and has a female:male ratio of 9:1.² Studies on geriatric populations have shown a prevalence of pSS of 1.9–4.8%.^{3–5} The estimated prevalence of pSS in the general population in Slovenia is 0.6%.⁶ After extensively reviewing published reports, we found only one study assessing the incidence of pSS diagnosed by a physician. The average annual incidence for pSS in Olmsted County, Minnesota, was 3.9 cases per 100 000 population.⁷

Our study aimed at estimating the annual incidence of pSS in the general population in Slovenia. All patients were evaluated using the European criteria for SS, which were the last validated criteria for SS in our study period.⁸

PATIENTS AND METHODS

Patients

We prospectively examined all patients admitted to our department of rheumatology or referred to our outpatient clinic between 1 January 2000 and 31 December 2002, mainly because of sicca symptoms. To increase recruitment, all ophthalmologists in the Ljubljana region were informed of this study and asked to direct patients with symptoms of dry eyes (irritation, grittiness, and foreign body sensation) to our outpatient clinic. Additionally, all patients initially referred to our department with other suspected diagnoses, but indicated by our rheumatologists for SS diagnostic tests based on medical history, clinical examination, and/or serological results, were included during the above period. Ours is the only rheumatological department or outpatient clinic in the

Table 1 Referring physicians and suspected diagnoses of the evaluated patients

	General practitioners	Specialists of internal medicine	Ophthalmologists	Otorhynolaryngologists	Oral surgeons	Other specialists	Total No (%)
Sicca complex	92	11	12	2	1	9	127 (51.2)
Arthritis/ arthralgias	43	2	0	0	0	9	54 (21.8)
Suspected CTD	17	8	0	0	0	5	30 (12.1)
Fibromyalgia	7	1	0	0	0	4	12 (4.8)
Parotitis	2	0	0	2	1	1	6 (2.4)
Other diagnoses	15	3	0	0	0	1	19 (7.7)
Total, No (%)	176 (71.0)	25 (10.1)	12 (4.8)	4 (1.6)	2 (0.8)	29 (11.7)	248 (100)

arthralgias. The majority of patients (71.0%) were referred by general practitioners, while ocular and oral specialists sent only 7.2% of patients (table 1).

Table 2 shows a comparison of the clinical, laboratory, and other characteristics of SS in patients with and without pSS.

Minor salivary gland biopsy was performed in all 36 patients positive for anti-Ro antibodies. Twenty five of them proved to have positive histopathology with an average focus score of 2.5 (range 1–6), while in 11 patients the result was negative. Among 39 positive histological results, the average focus score was 1.8 (range 1–6).

Eleven of 71 (15%) patients diagnosed with pSS were active smokers at the time of the study and three (4%) were former smokers. Among 177 patients not labelled as having pSS, 34 (19%) were smokers on the evaluation, while 17 (9.6%) stopped smoking before the start of the study.

Based on the catchment population, the average annual incidence for pSS in the Ljubljana region was calculated as 3.9 cases per 100 000 inhabitants (exact 95% CI 1.1 to 10.2). This figure may be extrapolated to the whole country, because the Slovenian population is demographically homogeneous.

DISCUSSION

The main purpose of our study was to determine the annual incidence of pSS in Slovenia. As far as we know, this is the first report on the incidence of pSS, employing the validated European classification criteria for SS⁸ in a prospective evaluation of all suspected subjects. We chose the European diagnostic criteria as they were the most recent validated criteria for SS in our study period, their validation was based

on a multicentre European study, and they are well defined.^{8,12} The presence of four of the six items of the criteria set classifies subjects as definite SS.⁸

The average annual incidence of pSS in Slovenia was assessed to be 3.9 per 100 000 population.

We found only one study reporting the incidence of pSS diagnosed by a physician.⁷ The average annual incidence for pSS in Olmsted County, Minnesota, was estimated as 3.9 cases per 100 000 population⁷—exactly the same as in our study. These identical results are somewhat surprising as the study designs and methodologies differed.

We prospectively examined all subjects referred to our tertiary (and the only regional) rheumatological centre owing to sicca symptoms. In addition, patients originally assigned other referral diagnoses, but subsequently suspected to have SS, were also included in the evaluation. The American study was retrospective, based on a review of all medical records of residents in Olmsted County with SS diagnosed by a physician. To identify possibly misclassified cases, all records from patients with xerostomia or keratoconjunctivitis sicca were also reviewed.⁷ With this approach, they covered the region of approximately 100 000 inhabitants, whereas the general population in the Ljubljana region, gravitating to our centre, is six times bigger (about 600 000 residents). There was also a significant difference in the observational period: 3 years in our study (1 January 2000–31 December 2002) and 16 years in the American study (1976–1992). Finally, we used well defined and validated European classification criteria to diagnose SS,⁸ which was not the case in the American study.

Additionally, the age and sex ratio differed. The mean age at the diagnosis of pSS was 51 years in our patients and 60 years in Pillemer's study. We had a female:male ratio of 11:1, whereas it was somewhat higher (13:1) among the American patients. It is worth mentioning that in both studies all patients were Caucasian subjects.

In general, there are two major problems in estimating the incidence of pSS. The first is that patients often delay seeking medical help for substantial periods of time after the onset of symptoms. People with mild disease may not have sought medical attention, or the diagnosis may not have been suspected or established even if they were seen by a physician. The average duration from the beginning of symptoms to diagnosis was 4.9 years (range 2 months to 15 years) in our study. This figure probably reflects well the actual situation in Slovenia.

The second problem concerns the case definition of pSS. In particular, pSS is a disease for which different diagnostic criteria have been proposed. Consequently, studies using differing diagnostic measures are not easily comparable.¹³

A potential bias in our study may have been the lack of promoting recruitment at otorhynolaryngologists, dentists, and oral surgeons. However, we believe that patient enrolment was close to optimum, based on the organisation of the health system in Slovenia: there is "free" (at no cost) access

Table 2 The presence of clinical, laboratory, and other characteristics of Sjögren's syndrome (SS) in patients diagnosed with primary SS and those not fulfilling the validated European classification criteria for SS⁸

Characteristics	With pSS (n = 71)		Without pSS (n = 177)	
	No (%)	ND (%)	No (%)	ND (%)
Ocular symptoms	64 (90)	0	133 (75)	0
Oral symptoms	62 (87)	0	128 (72)	0
Schirmer-I test*	20 (28)	0	30 (17)	0
Rose bengal score	55 (79)	1 (1)	60 (34)	2 (1)
USF*	29 (41)	1 (1)	65 (37)	2 (1)
Salivary scintigraphy	55 (89)	9 (13)	53 (44)	56 (32)
Histopathology	39 (59)	5 (7)	3 (3)	73 (41)
ANA	58 (82)	0	72 (41)	1 (0.6)
Anti-Ro	36 (51)	0	7 (4)	1 (0.6)
Anti-La	16 (23)	0	1 (0.6)	1 (0.6)

ANA, antinuclear antibodies; USF, unstimulated salivary flow test; ND, not done.

*The results were considered positive only in patients younger than 60 years.

to general practitioners and specialists, the referral rate to specialists is very high, and it is highly unlikely that any patient would seek medical help for possible SS in another Slovenian region or abroad.

Possibly, some patients with pSS were missed because they smoked, which might have lowered focus scores and negatively influenced the determination of anti-Ro and anti-La antibodies.¹⁴

Considering the design of our study and the high ethnical homogeneity of the Slovenian population, we believe that our results are reliable. Additional larger epidemiological studies are needed, however, to estimate the incidence of pSS in different populations.

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