Epidemiology of Sjögren's syndrome: where are we now?

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Primary Sjögren's syndrome (pSS) is an autoimunne disease characterized by lymphocytic infiltration of the exocrine glands. Keratoconjunctivitis sicca and xerostomia related to lachrymal and salivary gland infiltration, respectively, are the main clinical manifestations. Asthenia may be present also. However, symptoms vary widely across patients in their nature and severity, a fact that hinders case ascertainment. Diagnostic criteria for pSS are required by both physicians and patients in order to provide a rational basis for their symptoms, assess their prognosis and guide therapy. Several different criteria sets have been proposed, varying in their emphasis predominantly on laboratory test, on clinical features of dry eye and dry mouth or on both. Recently, the American-European Consensus group have published revised criteria (AECC criteria) (1) making epidemiological studies timely. The few epidemiological studies of pSS in the general population yielded highly heterogeneous results, probably because of differences in diagnostic criteria and study design. As a result, the prevalence and incidence of pSS in the general population are unclear. Accurate estimates of these two epidemiological parameters would help to assess the public health burden caused by pSS.

To estimate the prevalence and incidence of pSS in the general population, we have performed a systematic review of published epidemiological studies of pSS. To determine the best study design for investigating the epidemiology of pSS, we have also evaluated the validity of screening questionnaires used in those studies.

The Pubmed and EMBASE databases were searched using the term "Sjögren's syndrome" in conjunction with the terms "prevalence" and "incidence". All publications published between January 1966 and June 2006 were considered. In the Pubmed data-base, we also used "Sjögren's syndrome/Epidemiology (Majr)" for the same time period, and we introduced the following limits: publication in English, French, or Spanish; and adults only. Reference lists from selected publications were screened for additional relevant studies. The abstract databases of the American College of Rheumatology and European League against Rheumatism meetings held in 2004 and 2005 were searched.

The abstracts of the publications retrieved by the search strategy were used to select publications relevant to the study. The full-length versions of these publications were printed out and reviewed in detail. We did not use validated instruments to assess the quality of the selected studies. For each selected publication, the following were recorded on a standardized form: authors' names, year of publication, journal, country where the study was performed, whether the study was population-based, population size, whether initial screening for pSS relied on a questionnaire, the diagnostic criteria set used, number of patients with pSS, and calculated prevalence or incidence. When a questionnaire was used for initial screening, we computed the positive predictive value (PPV) of questionnaire replies suggesting pSS.

The publication flow chart is shown in Figure 1. The Pubmed search retrieved 162 publications. No additional publications were found in EMBASE. Based on the abstracts, we excluded 132 publications. The remaining 30 publications were read in their full-length version, which led to exclusion of 15 additional publications. Two abstracts were retrieved from the EULAR meeting database. Thus, 17 publications were included in the study (2-18). Among them, 14 dealt with pSS prevalence, 2 with pSS incidence, and 1 with both.

Table I presents the main results of the 13 population-based studies (2-14). Studies that used more than one set of diagnostic criteria are listed once for each set. The prevalence estimates varied widely, from 0.092% to 3.59%. Nevertheless, 14 of the 17 prevalence estimates were lower than 2% and 12 were lower than 1%. In the three studies that evaluated the incidence of pSS in the general population, values ranged from 3.9 to 5.3 per 100,000 population.

Four studies were not conducted in the general population. Three studies were conducted in geriatric populations. Pre-

valence estimates in these studies were 3.3% in 122 individuals older than 80 years (15), 2% in 103 elderly Caucasian women (16), and 4.8% in 62 individuals older than 65 years (17). Using the AECC criteria (1), the prevalence of pSS was estimated at 2.7% of 300 ambulatory patients attending a tertiary care centre (18).

A questionnaire was used to screen for pSS in six studies, several of which used two or more diagnostic criteria sets, so that the total number of estimates obtained after questionnaire screening was 11. As shown in Table II, the PPVs of questionnaire replies suggesting pSS were low and varied widely, from 0.51% to 66.67%. PPV values were lower than 50.00% in 9 of 11 cases and lower than 10.00% in 8 of 11 cases.

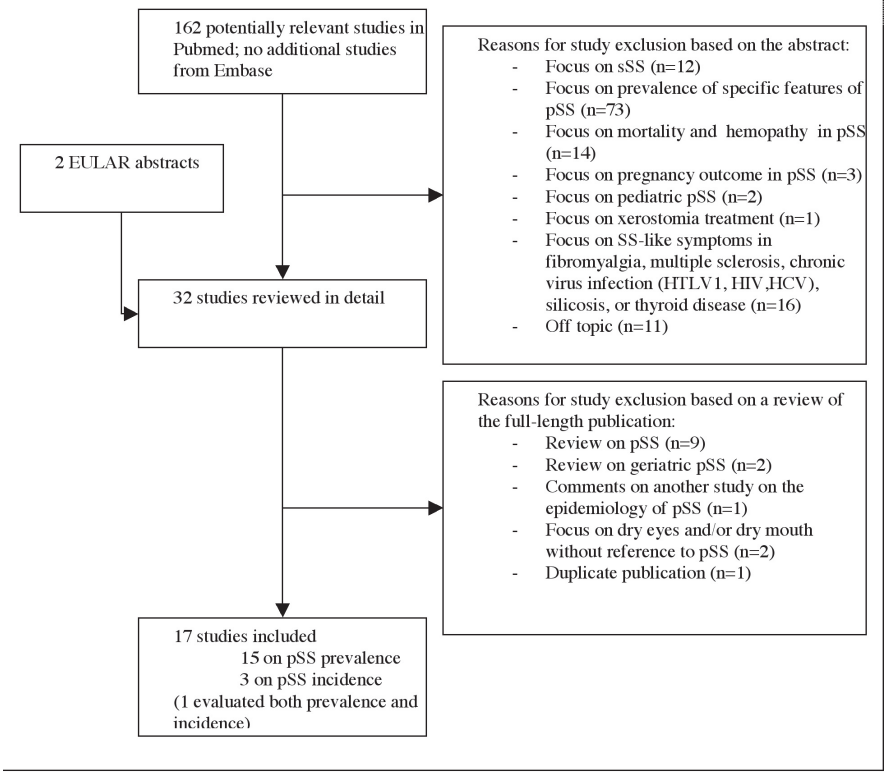
Although pSS is considered a common connective tissue disease, the few epidemiological studies conducted in the general population yielded highly variable prevalence and incidence estimates. The many methodological differences among studies hinder comparisons of results. A major obstacle to comparisons is that the diagnostic criteria for pSS have evolved over time, with the result that the diagnostic criteria sets varied across studies. The American-European Consensus group recently (2002) published revised criteria that constitute an appreciable advance but leave room for further improvement (1). Many studies are biased by a low response rate to the invitation to participate, usually only about one-third of the target population. Furthermore, some patients with a positive screening result probably declined further testing. Autoantibody assays, lip biopsy, parotid gland sialography, and salivary scintigraphy involve discomfort and/or a risk of adverse events and are therefore likely to be refused by individuals who will derive no individual benefit from them.

Incidence estimates are even more difficult to obtain than prevalence estimates, since the onset of the pSS is difficult to pinpoint. The symptoms are generally insidious and subjective. The time from symptom onset to the diagnosis of pSS has been reported to vary widely, from 2 months to 15 years (14). Available data suggest that the prevalence of pSS may be 0.5% to 1% in the general population in Europe. Further epidemiological studies are needed to improve the accuracy of this estimate. Studies in geriatric populations found higher prevalences of pSS than those done in the general population. This result is probably ascribable to a combination of age-related gland atrophy and drug-induced dryness of the mouth.

The questionnaires used to screen for pSS had low PPVs. In all but one study, the PPV was less than 50%, indicating that many individuals were offered testing for pSS although they did not have the disease. Nevertheless, the available data do not allow an evaluation of the sensitivity or specificity of the questionnaires, and the diagnostic usefulness of a test is difficult to assess based only on the PPV. For future studies, we suggest preliminary testing of the screening questionnaire by comparing the replies given by controls and by patients with pSS. Alternatively, the catch-recatch method could be used to evaluate the prevalence of pSS in well-defined geographic regions where medical care is well organized and readily accessible. The socioeconomic characteristics of the population in the region should reflect that of the general population if this method is to be relevant.

In conclusion, although the exact prevalence and incidence of pSS remain unclear, the prevalence can be estimated at 0.5%-1%. Because pSS causes major deteriorations in quality of life, further epidemiological studies are needed (11). Although there is no "cure" for pSS patient's symptoms, the detection of cases remains important: Firstly, these patients may be significantly improved by measures aimed at prevention of ocular and dental complications and by the recognition of extraglan-

Fig. 1. Flow chart of studies retrieved from Pubmed and EMBASE; and from EULAR, ACR, and SFR abstract databases. Studies were selected based on presence of information on the prevalence and incidence of primary Sjögren's syndrome.



EULAR: European League against Rheumatism; ACR: American College of Rheumatology;SFR: Société Française de Rhumatologie (French Society for Rheumatology); pSS: primary Sjögren's syndrome; sSS: secondary Sjögren's syndrome.

Table I. The thirteen studies on the prevalence and/or incidence of primary Sjögren's syndrome in the general population retrieved by our search strategy. Studies that used several diagnostic criteria sets are listed once for each set.

Year, country (reference no)	Diagnostic criteria	Population size (n)	Prevalence % (95% CI)	Incidence per 10^5 (95% CI)
2006, Greece (2)	AECC	488 435	0.092 (0.08-0.10)	5.3 (4.5-6.1)
2004, UK (3)	AECC	548	0.4 (0.04-1.32)	-
2005, Greece (4)	AECC	8740	0.15 (0.09-0.21)	-
1997, Denmark (5)	Copenhagen	499	0.2 to 0.8	-
2004, Turkey (6)	AECC	2835	0.21 (0.08-0.46)	-
1995, China (7)	San Diego	2066	0.34 (0.44-1.25)	-
2004, Turkey (6)	European	2835	0.35 (0.17-0.65)	-
1997, Denmark (5)	European	499	0.6 up to 2.1	-
1999, Slovenia (8)	European (definite pSS)	339	0.6 (0.07-2.16)	-
1997, Greece (9)	European (definite pSS)	837	0.6 (0.19-1.39)	-
2004, Turkey (10)	AECC	939	0.6 (0.24-1.39)	-
1995, China (7)	Copenhagen	2066	0.77 (0.44-1.25)	-
2004, Turkey (10)	Revised Japanese criteria	939	1.4 (0.74-2.37)	-
2004, Turkey (10)	European	939	1.5 (0.85-2.57)	-
1998, UK (11)	European	616	2.1 (1.13-2.58)	-
1989, Sweden (12)	Copenhagen	705	2.7 (1.0-4.5)	
1997, Greece (9)	European (definite/probable pSS)	837	3.59 (2.43-5.08)	-
2001, USA (13)	Physician diagnosis from 1976 to 1992	~100 000	-	3.9 (2.8-4.9)
2004, Slovenia (14)	European	241	-	3.9 (1.1-10.2)

95%CI: 95% confidence interval; AECC: American European Consensus Criteria; pSS: primary Sjögren's syndrome.

Table II. Positive predictive value of the study with a first screening phase with a questionnaire.

Ref (n°)	Diagnostic criteria	Population size (n)	Questionnaire+ (n)	FP (n)	TP (n)	PPV (%)
(5)	Copenhagen	499	189	188	1	0.53
(5)	European	499	189	186	3	1.59
(10)	AECC	939	186	180	6	3.23
(6)	AECC	2835	159	153	6	3.77
(11)	European	616	341	328	13	3.81
(6)	European	2835	159	149	10	6.29
(10)	Revised Japanese criteria	939	186	173	13	6.99
(10)	European	939	186	172	14	7.53
(9)	European (definite SS)	837	45*	30	5	11.11
(3)	AECC	548	4	2	2	50.00
(9)	European (definite/probable SS)	837	45*	5	30	66.67

FP: False positive; TP: True positive, PPV: positive predictive value.
*In this study, 10 of 45 women refused further testing; in order to obtain a conservative (lower) PPV estimate for this study, we considered that all 45 women had false-positive questionnaires.

dular features that may be amenable to specific treatment. Secondly, given to the knowledge about physiopathology (19), it is to be hoped that randomized controlled trials of the efficacy and safety of biologics, including anti B therapy, will be available soon in recent and severe pSS (20).

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