Are There Clinical or Serological Differences Between Male and Female Patients with Primary Sjögren's Syndrome?

CÉSAR DÍAZ-LÓPEZ, CARME GELI, HÈCTOR COROMINAS, NÚRIA MALAT, CÉSAR DIAZ-TORNER, JOSEP MARIA LLOBET, ARTURO RODRIGUEZ DE LA SERNA, ANA LAIZ, MIREIA MORENO, and GUILLERMO VÁZQUEZ

ABSTRACT. ***Objective.*** Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease. It can be primary (pSS) or secondary (sSS) and is observed 90% more in women than in men, mainly in the fourth and fifth decades of life. We investigated the prevalence of serological and clinical manifestations in male and female patients with primary SS.

Methods. We analyzed 521 female and 28 male patients with pSS between 1993 and 2001. All patients fulfilled ≥ 4 of the 1993 European Community Study Group criteria.

Results. Men presented higher concentrations of IgA, rheumatoid factor, and antinuclear antibodies than women. A higher percentage of women than men reported fibromyalgia, thyroidal manifestations, and carpal tunnel syndrome. There were no statistical differences between the 2 groups in relation to the presence of Raynaud's phenomenon, arthritis, erosive osteoarthritis, liver disease, or other visceral manifestations.

Conclusion. The pattern of SS in our cohort of patients reveals a difference between male and female patients, in contrast with earlier studies. (J Rheumatol 2004;31:1352–5)

Key Indexing Terms:
SJÖGREN'S SYNDROME AUTOIMMUNITY SEX DIFFERENCES

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease of unknown etiology that is characterized by lymphocytic infiltration of exocrine organs leading to glandular dysfunction. It may be primary (pSS) or secondary (sSS) to other connective tissue disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis, or progressive systemic sclerosis. SS is commonly associated with extraglandular abnormalities including organ-specific diseases such as thyroid, kidney, and lung diseases or with a non-organ-specific pattern affecting muscle, joints, and skin. It is seldom associated with hematological disorders. The prevalence of SS in the general population ranges from 0.6% to 3%, with a higher prevalence in women[1,2].

The etiology of SS includes both constitutional and environmental factors, leading to autoimmunity. Constitutional factors include hormones and multiple genes, and the environmental factors are mainly viral. The clinical abnormalities are mediated by cell infiltrates and cytokine activity, but immune complexes with vasculitis may also play a role. The serologic changes most commonly seen in pSS are hypergammaglobulinemia, the presence of paraproteins, and diverse autoantibodies — rheumatoid factor (RF), antinuclear antibodies (ANA), and anti-SSA/Ro and anti-SSB/La[3].

Four groups of male patients with pSS have been characterized and compared with female patients on the basis of clinical and laboratory findings. Molina, *et al*[4] compared 36 men and 69 women and found no clinical differences, but they observed that women presented a higher frequency of positive RF and anti-SSA/Ro. However, Anaya, *et al*[5] examined 13 men and 25 women, and found that although men were more likely to present extraglandular manifestations, there were no significant differences in the laboratory variables between the sexes. In a study of 12 men and 30 women, Drosos, *et al*[6] reported a higher frequency of arthritis and Raynaud's phenomenon and more ANA and Ro antibodies in the women. By contrast, in a group of 14 men and 28 women Brennan, *et al*[7] showed greater fatigue and more serological abnormalities in the female group. Although these investigators found a greater frequency of abnormal ANA and anti-SSA/Ro in women, the presence of extraglandular abnormalities is still unclear.

We investigated the clinical and serologic characteristics of 521 women and 28 men with pSS to gain insight into this disorder.

From the Unitat de Reumatologia, Departament de Medicina Interna, Hospital de la Santa Creu i Sant Pau; and the Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Catalonia, Spain.

C. Díaz-López, MD; C. Geli, MD; H. Corominas, MD; C. Diaz-Torner, MD; J.M. Llobet, MD; A. Rodriguez De La Serna, MD; A. Laiz, MD; M. Moreno, MD; G. Vázquez, MD, Departament de Medicina Interna, Hospital de la Santa Creu i Sant Pau; N. Malat, MD, Institut Municipal d'Investigació Mèdica.

Address reprint requests to Dr. H. Corominas, Unitat de Reumatologia, Departament de Medicina Interna, Avda. San Antoni M. Claret, 167, 08025 Barcelona, Catalonia, Spain. E-mail: hcorominas@hsp.santpau.es

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MATERIALS AND METHODS

Data were collected from more than 550 outpatients with pSS between 1993 and 2001 at the Rheumatology Unit of the Internal Medicine Department, Sant Pau University Hospital, Barcelona. Only 28 consecutive male patients were diagnosed and followed during this period. All the patients presented subjective and objective keratoconjunctivitis sicca and xerostomia. A minor labial salivary gland biopsy was taken from patients (except 74 patients who refused), and immunological and basic laboratory tests were performed. The control group consisted of 521 female patients matched according to the same criteria used for the male patients. All patients fulfilled ≥ 4 of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993, and diagnostic tests were applied according to the recommendations of the European Community Study Group[8]. Fibromyalgia (FM) was assessed by the American College of Rheumatology (ACR)-90 criteria[9]. Immunological tests included serum immunoglobulins, RF by nephelometry, ANA by indirect immunofluorescence using HEp-2 cells, antithyroid antibodies employing immunofluorescence, and SSA/Ro and SSB/La using ELISA.

Data are presented as means and percentages. Differences between means and proportions were established using the 2-tailed Mann-Whitney U test and Fisher's exact test when appropriate. The statistical analysis comparing men with women was performed with the Epi-Info statistical package. A p value < 0.05 was considered statistically significant.

RESULTS

The comparison of demographic data between men and women did not show any statistical differences. Parotidomegalia was similar in both groups, whereas the sicca syndrome was the most frequently observed symptom at the onset of the disease. Demographic findings and characteristics of extraglandular diseases and clinical manifestations from patients are shown in Table 1.

A significantly higher percentage of women reported FM (p = 0.001), thyroidal manifestations (p = 0.006), and carpal tunnel syndrome (CTS; p = 0.02) compared with men. There were no statistical differences between the 2 groups in relation to the presence of Raynaud's phenomenon, arthritis, erosive osteoarthritis, liver disease, and other visceral manifestations.

Immunological tests in our population showed significant differences between sexes; men presented higher concentrations of IgA (p = 0.004), RF (p = 0.04), and ANA (p = 0.02) than women. The presence of immunoglobulins, cryoglobulins, and anti-SSB/La was similar in both groups (Table 2).

DISCUSSION

Primary Sjögren's syndrome (pSS) in men is rare[10]. The female/male ratio is 9/1, although in our study it reached 18/1. Results from earlier studies to evaluate sex differences are inconsistent with the prevalence of extraglandular manifestations and immunological tests (Table 3). Our results concerning the presence of extraglandular manifestations

Table 2. Immunological tests in the patients with SS.

	Males (%)	Females (%)	p
IgG > 1700 mg/100 ml	7 (25)	63 (12)	NS
IgA > 390 mg/100 ml	11 (39.2)	81 (15.5)	0.004
IgA < 60 mg/100 ml	0 (0)	8 (1.5)	NS
IgM > 250 mg/100 ml	2 (7.1)	43 (8.2)	NS
IgM < 40 mg/100 ml	1 (3.5)	11 (2.1)	NS
Rheumatoid factor, IU/ml	13 (46.4)	149 (28.5)	0.04
Antinuclear antibodies > 1/80	22 (78.5)	311 (59.6)	0.02
Antithyroid antibodies	2 (7.1)	142 (27.2)	0.02
Anti-SSA/Ro antibodies	7 (25)	96 (18.4)	NS
Anti-SSB/La antibodies	4 (14.2)	47 (9)	NS

Table 1. Demographic and clinical data of patients with SS.

	Male (%)	Female (%)	p
No. of patients	28	521	
Median age, yrs	63.5	64	NS
Q1	55.3	55	
Q3	63.5	72	
Outcome (years)	4.5	7	NS
Q1	2	4	
Q3	9	12	
Parotidomegalia	5 (17.8)	76 (14.5)	NS
Raynaud's phenomenon	5 (17.8)	145 (27.8)	NS
Carpal tunnel syndrome	4 (14.2)	208 (39.9)	0.02
Arthritis	8 (28.5)	185 (35.5)	NS
Monoarthritis	5 (17.8)	25 (4.7)	
Oligoarthritis	3 (10.7)	50 (9.5)	
Polyarthritis	0 (0)	110 (21)	
Erosive/inflammatory osteoarthritis	3 (10.7)	55 (10.5)	NS
Fibromyalgia	2 (7.1)	199 (38)	0.001
Thyroidopathy	1 (3.5)	137 (26.2)	0.006
Liver diseases*	1 (3.5)	2 (3.8)	NS
Other clinical visceropathy	0 (0)	30 (5.7)	NS

* Patients with B and C hepatitis or biliary cirrhosis were excluded. Two-tailed Mann-Whitney test and Fisher exact test. p < 0.05 was considered statistically significant. Q: quartile.

Table 3. Comparison of significant results in studies of clinical and immunological characteristics of male and female patients with primary SS.

Study	F/M	Extraglandular Manifestations	Immunological Tests
Molina[4]	69/36	No differences	More frequent RF and anti-Ro in women
Anaya[5]	25/13	No differences	No differences
Drosos[6]	30/12	More arthritis and RP in women	More frequent ANA and anti-Ro in women
Brennan[7]	28/14	More fatigue in women	More frequent: ESR, ANA, and IgG in women
Present study	521/28	More FM and thyroidal disorders in women	More frequent antithyroid Ab in women More RF, ANA, and IgA in men

RF: rheumatoid factor, ANA: antinuclear antibodies, ESR: erythrocyte sedimentation rate, RP: Raynaud's phenomenon, FM: fibromyalgia.

reveal a higher female prevalence of FM (39.6% vs 7.1%; p = 0.001), CTS (41.6% vs 14.3%; p = 0.02), and thyroid disorders (27.2% vs 3.6%; p = 0.006) (Table 1).

Brennan, *et al*[7] found more clinical fatigue in female patients. The higher prevalence of extraglandular manifestations (FM, CTS, and hypothyroidism) in women supports the view that extraglandular manifestations could be sex related instead of pSS related[9,11,12]. In contrast to Drosos, *et al*[6], we found no difference in arthritis or Raynaud's phenomenon.

Immunological and serological abnormalities in pSS are more frequent in women. Moreover, higher levels of erythrocyte sedimentation rate (ESR), immunoglobulin IgG, RF, ANA, anti-SSA/Ro or anti-SSB/La have been described in women[4,6,7].

Interestingly, given that autoimmune diseases are more prevalent in women, estrogens appear to be immunostimulatory, whereas androgens could play an immunoinhibitory role. Women produce more autoantibodies and a greater cell mediated response than men. Studies in patients with SLE and RA attribute such a role to hormones, but few studies support a lower androgen level in women with pSS[9,12,13]. Sex related differences suggest that the expression of pSS is influenced by various sex hormones[14]. Patients with pSS have moderately increased levels of prolactinemia, which is especially evident in individuals diagnosed at an early age[15,16].

Our findings are controversial because of the higher prevalence of elevated RF, ANA, and IgA in men than in women. We found a higher prevalence of elevated antithyroid antibodies, FM, and thyroidal disorders in women (Table 2). We attribute the differences in our study to a number of factors: (1) The mean age of men and women in our sample was older than in other studies. Patients in other studies were pre- or perimenopausal, and in our study all women were postmenopausal. (2) Our study was performed in a small sample of men with pSS. We therefore suggest that prospective clinical trials should be undertaken in a larger group of men with pSS to account for these results. (3) There is evidence that estrogens and other hormones have a biphasic dose effect, with low doses inducing the disease and high doses protecting against it[17]. This would explain the controversy in experimental studies with estrogens[18,19]. Further studies using the new USA-EU criteria would be of interest to reach a consensus on primary Sjögren's syndrome[20].

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