Lower prevalence of extra-glandular manifestations and anti-SSB antibodies in patients with primary Sjögren's syndrome and widespread pain: evidence for a relatively benign subset

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Abstract

Objectives

To investigate in primary Sjögren's syndrome, the differences between patients with and without widespread pain (WSP) with respect to the cumulative prevalence of extra-glandular manifestations (EGMs) and systemic auto-antibodies.

Methods

All outpatients diagnosed with primary Sjögren's syndrome (2) were included in a prospective follow-up, with at least one check up each year, from June 1991 until November 2011. Patients who also fulfilled criteria for concomitant connective tissue disorders were excluded. Widespread pain was defined as the presence of long-lasting (>one year) diffuse pain in all four body quadrants. Data were collected with respect to the cumulative prevalence of systemic auto-antibodies (anti-nuclear antibodies [ANA], anti-Sjögren syndrome A antigen [anti-SSA], anti-Sjögren syndrome B antigen [anti-SSB] and immunoglobulin M-Rheumatoid factor [IgM-RF]) and EGMs related to primary Sjögren's syndrome.

Results

Eighty-three patients were included in the final analysis. Thirty-nine (34.9%) patients had widespread pain. Anti-SSB was found less frequently ($p<0.05$) in patients with WSP than in patients without WSP. The WSP-positive patients were more frequently negative for all four tested autoantibodies ($p<0.05$). The patients with WSP had fewer EGMs than the patients without WSP ($p<0.01$); more specifically, polyneuropathy occurred less frequently ($p<0.05$) in the patients with WSP. Cytopenia, uveitis, pericarditis, pleuritis, interstitial lung disease, vasculitis, monoclonal gammapathy of unknown significance and non-Hodgkin lymphoma only occurred in the patients without WSP.

Conclusions

Primary Sjögren's patients with WSP form a benign subgroup, with a lower prevalence of anti-SSB and EGMs (in particular polyneuropathy). We suggest a shorter period of follow-up for this subset than for the WSP-negative patients.

Key words

systemic auto-antibodies, extra-glandular manifestations, primary Sjögren's syndrome, widespread pain

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Introduction

Primary Sjögren's syndrome is an auto-immune disease of unknown etiology that is not accompanied by other connective tissue diseases (*e.g.* rheumatoid arthritis [RA] or systemic lupus erythematosus [SLE]). The condition is characterised by lymphocytic infiltrates and destruction of the salivary and lacrimal glands, leading to clinical signs of xerophtalmia, xerostomia and swelling of parotid glands. Additionally, systemic manifestations like neuropathy, interstitial lung disease and renal disease, as well as organ-specific auto-immune diseases like Hashimoto's thyroiditis and primary biliary cirrhosis may occur (1).

The presence of auto-antibodies is a hallmark of the disease, with the presence of anti-Sjögren syndrome A antigen (anti-SSA) and/or anti-Sjögren syndrome B antigen (anti-SSB) being a classification criterion (2). Recently, we published a paper on the positive association between anti-SSA antibodies and the number of extra-glandular manifestations (EGMs) in primary Sjögren's syndrome (3).

In primary Sjögren's syndrome, many patients exhibit rheumatological manifestations, such as (poly)arthritis, arthralgia, myalgia, etc. Some patients have generalised musculoskeletal pain, classified as a so-called widespread pain (WSP). Often, these patients fulfil the criteria for fibromyalgia syndrome (FMS) (4). We now investigated, in an outpatient (real life) setting, whether patients with WSP form a distinct (benign) subset with respect to EGM and serological profile.

Methods

The primary goal of this prospective and descriptive study was to investigate the prevalence of EGMs and systemic auto-antibodies in patients with primary Sjögren's syndrome, with or without WSP, attending our clinic (a large non-academic teaching hospital in the Netherlands).

For this purpose, all outpatients who had been diagnosed with primary Sjögren's syndrome between June 1991 and November 2011 were followed up by one (and the same) treating rheumatologist (EJtB). All patients were seen at least once a year with special focus on the presence of EGMs. Only patients fulfilling the 2002 European criteria for primary Sjögren's syndrome (2) were included in the analysis. Patients who also fulfilled criteria for concomitant connective tissue diseases (*e.g.* RA, SLE, systemic sclerosis, etc.) were excluded. Widespread pain was defined as the presence of long-lasting (>one year) diffuse pain in all four body quadrants, without the presence of arthritis. Most of these patients fulfilled the 1990 American College of Rheumatology (ACR) criteria for FMS (4) and all of the patients met the new preliminary ACR criteria for FMS (5).

Laboratory data concerning the presence of auto-antibodies (ANA, anti-SSA, anti-SSB and IgM-RF) and blood cell counts were collected from all patients. All laboratory tests were performed at the clinical chemistry or immunology laboratory at the St. Antonius Hospital. The presence of ANA was determined via indirect immunofluorescence tests on Hep-2 cells; a titer ≥1:80 on two separate occasions was considered positive. Two positive ELISA tests were considered a positive result for anti-SSA and anti-SSB antibodies. The presence of IgM-RF was determined via nephelometry (positive value ≥25, on two occasions). Leucopenia was defined as a leucocyte count below 3.0 x 10^9/L, trombocytopenia was defined as a platelet count below 100x10^9/L and haemolytic anaemia was defined as a haemoglobin level <6.0 x10^9/L with biochemical signs of hemolysis and a positive direct Coombs test. These abnormal cell counts had to be found on at least two separate occasions. All of the laboratory test data were complete for all of the patients.

Furthermore, medical charts were checked systematically for the cumulative prevalence of WSP, as well as for the cumulative prevalence of EGMs related to primary Sjögren's syndrome, in particular: cutaneous vasculitis, discoid lupus/subacute cutaneous LE, polyneuropathy (PNP; positive electromyography), interstitial lung disease (ILD; x-ray confirmed by high resolution computed tomography and/or histology),

pleuritis, renal tubular acidosis (RTA; laboratory parameters), uveitis, pericarditis (confirmed by echocardiography), cerebral Sjögren (with compatible MRI findings), monoclonal gammapathy of unknown significance (MGUS) and non-Hodgkin lymphoma.

For the purpose of analysis, if patients had concomitant conditions that could also (likely) account for the manifestation, this manifestation was not attributed to primary Sjögren's syndrome and the manifestation was regarded absent.

Data analysis

For descriptive statistics, we computed percentages, means (with standard deviations [SD]) and medians (with range), where appropriate. For the comparisons between groups, we used the Fisher's exact test for categorical variables and the Mann-Whitney-U test for ordinal variables.

To further explore the relation of WSP with EGM we performed a multivariate analysis to account for confounding variables. We chose the negative binomial regression to model the count of EGMs present in a patient as a function of WSP present or not, age and the duration of the disease.

Table I. Clinical and serological characteristics of included patients with primary Sjögren's syndrome (n=83).

Parameter	
Female, n (%)	74 (89.2%)
Mean age at diagnosis, years ± SD	54.3 ± 14.4
With WSP n (%)	29 (34.9%)
Caucasians, n (%)	74 (89.2%)
Disease duration in months, median (range)	87 (2-343)
Anti-SSB positive, n (%)	40 (48.2%)
Anti-SSA positive, n (%)	62 (74.7%)
Anti-SSA and/or anti-SSB positive, n (%)	66 (79.5%)
IgM-RF positive, n (%)	51 (61.4%)
ANA positive, n (%)	61 (74.4%)
All 4 auto-antibodies negative, n (%)	9 (10.8%)
All 4 auto-antibodies positive, n (%)	28 (33.7%)
Minor salivary gland biopsy, focus score ≥1 (performed in 73 patients), n (%)	63 (86.3%)

Table II. Serological data and clinical characteristics for the group with and the group without widespread pain (WSP).

	WSP -		WSP +		*p*-value
	n	%	n	%	
All cases:	54	–	29	–	–
Anti-SSA	43	79.6	19	65.5	0.1902
Anti-SSB	31	57.4	9	31.0	0.0373
Anti-SSA and/or SSB	45	83.3	21	72.4	0.2645
IgM-RF	33	61.1	18	62.1	1.0000
ANA	40	75.5	21	72.4	0.7953
All four auto-antibodies positive	23	42.6	5	17.2	0.0279
All four auto-antibodies negative	4	7.4	5	17.2	0.2656
Xerophtalmia (subjective)	46	86.8	28	96.6	0.2491
Xerostomia (subjective)	53	98.1	28	96.6	1.0000
≥1 abnormal eye tests	42/53	79.2	21/29	72.4	0.5860
≥1 abnormal salivary tests	26/28	92.9	14/17	82.4	0.3504
Minor salivary gland biopsy, focus score ≥1	41/46	89.1	22/27	81.5	0.4834
Salivary scintigraphy positive	18/19	94.7	8/12	66.7	0.0600

Note: Serological and clinical characteristic categories are in accordance with Vitali *et al*. (2).

Results

Characteristics of the study subjects (Table I)

A total of 103 patients fulfilled the criteria for primary Sjögren's syndrome (2). Fourteen patients also fulfilled the criteria for RA, three for SLE, one for both RA and polymyositis, one for both RA and SLE, and one for incomplete CREST syndrome. These patients were excluded. A total of 83 patients were included in the final analysis. These subjects were predominantly female (89.2%) and the mean age was 54.3 years at the time of diagnosis. The median disease duration (*i.e.* follow-up) was 87 months (range: 2–343 months). The cumulative follow-up was 693 patient years. Most of the patients were Caucasian (n=74; 89.2%). Thirty nine (34.9%) patients had widespread pain.

Systemic auto-antibodies were abundant: 79.5% of patients were positive for either anti-SSA or anti-SSB. Only 9 (10.8%) patients tested negative for all of the screened systemic antibodies. Xerophtalmia was present in 90.2% and xerostomia was present in 97.6% of the patients. Ocular diagnostic tests (either Schirmer's test and/or Rose Bengal score) were positive in 77.8% of the patients (one patient refused ocular tests). Salivary gland involvement (abnormal unstimulated whole salivary flow and/or parotid sialography and/or salivary scintigraphy) was identified in 40 of the 45 (88.9%) tested patients. In 73 patients, minor salivary gland biopsies had been performed, and 63 (86.3%) of these had a focus score ≥1. Six cases had ILD, with a pattern of non-specific interstitial pneumonia (NSIP) on high resolution CT scan in 4 cases. The other two cases presented with a lymphocytic interstitial pneumonia (LIP) pattern and an unspecified pattern.

We saw sixteen cases with polyneuropathy, mostly (n=7) axonal sensorimotor PNP. One case only had sensory PNP, one only had motor PNP, two had an undefined (axonal) PNP, and three had evidence of a so called small fiber PNP (with normal EMG findings).

Differences between patients with and without WSP (Tables II and III)

The prevalence of anti-SSB was less in patients with WSP ($p<0.05$) than in patients without WSP. There were no differences with respect to the presence of anti-SSA, RF or ANA. The WSP-positive patients were more frequently negative for all four tested autoantibodies ($p<0.05$). There was a trend of fewer abnormal salivary glands scintigrams

Table III. Extra-glandular manifestations (EGMs) in the group with and the group without widespread pain (WSP).

EGM	WSP -		WSP +		*p*-value
	n	%	n	%	
EGM [mean number (SD) /case]	0.85 (1.07)	–	0.28 (0.53)	–	0.0065
At least one EGM	29	53.7	7	24.1	0.0113
Cytopenia*	7	13.0	0	0.0	0.0901
Cerebral Sjögren	0	0.0	1	3.4	0.3494
Uveitis	1	1.9	0	0.0	1.0000
Discoid LE/SCLE	4	7.4	4	13.8	0.4412
Pleuritis	2	3.7	0	0.0	0.5398
Pericarditis	2	3.7	0	0.0	0.5398
Polyneuropathy	14	25.9	2	6.9	0.0432
RTA	1	1.9	1	3.4	1.0000
ILD	6	11.1	0	0.0	0.0867
MGUS	5	9.3	0	0.0	0.1572
Non-Hodgkin lymphoma	1	1.9	0	0.0	1.0000
Vasculitis	3	5.6	0	0.0	0.5483

*Auto-immune haemolytic anaemia (n=1) and/or trombocytopenia (n=1) and/or leucopenia (n=5) (see Methods section); RTA: renal tubular acidosis; ILD: interstitial lung disease; LE: lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; MGUS: monoclonal gammapathy of unknown significance.

in the WSP-positive cases (p=0.06). The patients with WSP had less EGMs than the patients without WSP (mean: 0.28 *vs*. 0.85 EGMs per patient; p<0.01, see Table II). With respect to the particular EGMs: polyneuropathy occurred less frequently (p<0.05) in the patients with WSP. Cytopenia, uveitis, pericarditis/pleuritis, ILD, vasculitis, MGUS and non-Hodgkin lymphoma only occurred in the patients without WSP. The prevalence of auto-immune thyroiditis was lower in the WSP positive group compared to the WSP negative group (data not given).

In order to control for potential confounding the multivariate negative binomial regression model showed a comparable effect of WPS on number of EGMs with or without controlling for duration of disease and age (data not shown).

All the five MGUS cases had paraprotein levels of <10 g/l. The patients with non-Hodgkin disease had a mucosa-associated lymphoid tissue (MALT) lymphoma in both parotid glands with a maximal paraprotein level of 16.2 g/l (IgG kappa).

Discussion

Our patient group represents a fair sample of the general population of patients with Sjögren's syndrome, as shown by the demographic characteristics. In our study group, 89.2% of patients with primary Sjögren's syndrome were female, which is consistent with the reported female preponderance of 90% (6). The mean age at the time of diagnosis was 54.3 years and is comparable to other reports (6-8).

The prevalence of EGMs was more or less comparable to the known prevalence in patients with primary Sjögren's syndrome (6). Most notably, arthritis did not occur in our study group because of the exclusion of patients who also fulfilled ACR criteria for rheumatoid arthritis (n=13). We excluded these patients in order to avoid contamination with patients with secondary Sjögren's syndrome associated with rheumatoid arthritis. Cutaneous vasculitis occurred less in our patients than recently shown in a large retrospective study (4% *vs*. 13%) (9).

FMS or FMS-like clinical symptoms frequently occur in primary Sjögren's syndrome. An Italian study reported a prevalence of 22% (10), a Chinese study found a prevalence of 14.3% (11), and an English study reported a prevalence of 12% (12). A very recent study from Italy reported on a prevalence of FMS of 18% (13). We preferred the term WSP over FMS because not all patients with generalised pain in all four body quadrants will fulfill the classification criteria for FMS, even though the clinical impact is the same. All of our patients met the new preliminary criteria for FMS (5). Recently, Yunus and Aldag stated that fulfillment of the 1990 ACR criteria is not necessary for a diagnosis of FMS in the clinic (14). The prevalence of WSP in our population was relatively high (35%), probably due to our high awareness of WSP.

There are hardly any studies on differences between primary Sjögren's syndrome with and without FMS with respect to serological abnormalities and EGMs. The Italian study found that the FMS subgroup showed less severe global involvement with less hypergammaglobulinemia, purpura, rheumatoid factor positivity and a lower frequency of a focus score ≥1 on lip biopsy (10). They suggested that the FMS patients form a benign subgroup.

Notably, we found that the WSP-positive patients less frequently had anti-SSB antibodies and EGMs compared to the WSP-negative cases. Within the EGMs, polyneuropathy (PNP) occurred less frequently in the WSP-positive group. The prevalence of PNP for our whole study population was higher (19.3%) than recently reported by the Ramos-Casals group (10%) (15). Many of the specified severe EGMs only occurred in the WSP-negative cases.

Conclusion

Primary Sjögren patients with WSP form a benign subgroup with a lower prevalence of anti-SSB and EGMs (in particular polyneuropathy). Based on this conclusion, we suggest a follow-up of the subset of Sjögren's syndrome with WSP at longer intervals than for the WSP-negative patients. Though not investigated in this study, we hypothesise that the risk of developing lymphoma will be very small in the WSP-positive subgroup due to a lower degree of polyclonal B cell (hyper) activity.

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