

A study of the arthritis pattern in primary Sjögren's syndrome

H.-J. Haga, E. Peen

Department of Rheumatology, Sydvestjysk Sygehus, DK-6720 Esbjerg, Denmark.
Hans-Jacob Haga, MD, PhD, Professor;
Elisabeth Peen, MD, PhD, Chief Consultant.

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Please address correspondence to:
Professor Hans-Jacob Haga,
Department of Rheumatology, Sydvestjysk Sygehus, DK-6720 Esbjerg, Denmark.
E-mail: HJH@ribeamt.dk

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ABSTRACT

Objective. To study the frequency and pattern of arthritis in primary Sjögren's syndrome (pSS), and its association with clinical and immunological factors.

Methods. 102 patients with pSS diagnosed according to the preliminary European Classification Criteria were examined yearly for 4.5 years in a prospective study design. Arthralgia and arthritis were registered during the 459 patient-years observation period.

Results. Arthralgia was reported by 75 patients (73.5%) and arthritis was demonstrated in 18 patients (17.6%) during the observation period. The most commonly affected joints were ankles ($n = 7$), MCP joints ($n = 6$), shoulders ($n = 6$), MTP joints ($n = 6$) and wrists ($n = 5$). Symmetrical bilateral arthritis were most commonly observed in ankles (4 patients) and wrists, shoulders and MTP joints. Five patients had long-standing arthritis observed at more than one clinical examination, and one developed seronegative rheumatoid arthritis. Arthralgia/arthritis was not correlated to any clinical or immunological factors, and usually ESR and CRP were normal when arthritis was observed.

Conclusion. Arthritis in pSS is usually mild, resolving, and unrelated to other clinical and immunological factors. A typical pattern is uni- and bilateral arthritis in the ankles, but joints in hands, feet and shoulders may also be affected.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease mainly affecting the salivary and lacrimal glands, resulting in functional impairment of these glands. The disease has various clinical manifestations, extending from organ-specific autoimmune exocrinopathy to systemic disease affecting several organs. Primary Sjögren's syndrome affects 0.29 - 4.8% of the population, the proportion being determined by the criteria used and the age group studied (1).

The disease has been characterized by a stable and rather mild course of glandular and extraglandular manifestations

(2). Several studies have described the extraglandular manifestations, and the incidence and prevalence varies mainly due to the use of different inclusion criteria and study designs (2-9). Most of these studies report high frequency of arthralgia in these patients, while the frequency of arthritis is lower and varies greatly. In a prospective study (2) following 31 patients with pSS for 10-12 years the investigators did not observe arthritis in any of the patients. In a Finnish prospective study they observed arthritis in 24% of 110 patients with pSS diagnosed in 1977-92 and followed to 1994-97 (6). Twenty-nine percent of elderly patients with disease onset after 70 years of age have been found to have articular involvement (9). We have previously found that arthritis was not more common in patients with early versus late onset of pSS – being 12.5% and 9.8% respectively (8) – confirmed by others (10). The pattern of arthritis and the association with immunological and clinical factors have not been studied, however.

In this study we have examined for arthritis in 102 patients with pSS in a prospective study design with a follow-up of 4.5 years (range 0.8 - 7.7 years). We have analyzed the pattern of arthritis and its association with immunological and clinical factors.

Patients, clinical recordings and analysis

The patients were diagnosed according to the preliminary classification criteria proposed by The European Classification Criteria Group (11). The pSS patients were examined at least once yearly during follow-up, and in addition to a physical and biochemical examination, they went through a structured interview screening for the presence and severity of disease manifestations.

Arthritis was defined as swollen and tender joint detected by clinical examination by a rheumatologist during follow-up.

One hundred and two patients participated in the study – 95 females and 7 males. The age at diagnosis was 53.4 years (range 19-78 years), and the age at start of the study was 57.4 years

(range 25-81 years). Follow-up was 53.4 months (range 10-92 months), and 62 patients were examined 4 times, 31 patients 3 times, and 9 patients 2 times during follow-up. A biopsy of the minor salivary glands of the lower lip had been performed in 91 of the 102 participating patients, and was evaluated with focus scoring according to the method described by Greenspan *et al.* (12).

Laboratory analysis was performed as previously described (13), and the serum level of IgA rheumatoid factor was analyzed by an ELISA method. Antibodies against cyclic citrullinated peptides anti-CCP were determined in the serum samples by the Elisa IgG system on the UniCAP 100 from Phramacia-Diagnostics. Measurement of keratoconjunctivitis sicca and xerostomia was performed as previously described (8, 13).

Statistical methods

Correlations between clinical variables were calculated by means of Spearman's rank correlation and Mann Whitney U test, and p-values < 0.05 were regarded as statistically significant.

Results

As demonstrated in Table I, 75 (73.5%) patients reported about arthralgia and arthritis was observed in 18 (17.6%) patients. During the observation period arthritis was observed in 25 out of 359 clinical examinations (7%), and the arthritis pattern is demonstrated in Table

II. The most commonly affected joints were the ankle (7 patients), MCP-joint (6 patients), shoulder (6 patients), MTP-joint (6 patients), and wrist (5 patients), while only 2 patients had arthritis in the knee and elbow respectively. Symmetrical bilateral arthritis were most commonly observed in the ankles (4 patients), wrist (3 patients), shoulder (1 patient) and MCP joints (2 patients). Five patients had arthritis at more than one clinical examination, and one of them (patient R) developed seronegative rheumatoid arthritis and was treated with NSAIDs, steroids and methotrexate. x-rays performed in patients with longstanding arthritis did not demonstrate erosions.

In 25 clinical examinations with arthritis, high sedimentation rate > 30 and high CRP > 10 was found in 4 and 5 examinations respectively.

By correlation analysis, there was no significant correlation of arthralgia and arthritis to the following clinical and immunological parameters: age at diagnosis, age at start of study, sex, months of follow-up, swollen salivary glands observed by the doctor or reported by the patient, high ESR > 30 mm and high CRP > 10 mg/liter, positive lip biopsy, ANA, anti-SSA/SSB, rheumatoid factor IgM and IgA, anti-CCP and serum level of immunoglobulin IgG. The correlations closest to reach significance was between arthritis and swollen salivary glands ($r = 0.19$; $p = 0.059$) and between arthritis and positive biopsy of the minor salivary glands ($r = 0.18$; $p =$

0.094). The correlation coefficient between arthritis and anti-SSA/SSB was -0.055 ($p = 0.59$).

Arthritis was treated with antimalarials ($n = 12$ patients), nonsteroidal antirheumatic drugs (NSAID) ($n = 5$), steroids ($n = 4$) and methotrexate ($n = 1$). Except for one patient who developed seronegative rheumatoid arthritis, all cases of arthritis went into remission.

Discussion

A typical arthritis pattern is often observed in rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus and sarcoidosis, but has not previously been described in primary Sjögren's syndrome (pSS). Our study demonstrate that both small finger joints and large joints such as ankle, shoulders, knees and elbows may be affected in pSS. Interestingly we demonstrated a relatively high frequency of uni- and bilateral ankle arthritis in pSS, like seen in sarcoidosis. Sarcoidosis is one of the differential diagnosis that has to be considered in the diagnosis of pSS due to sicca symptoms and sometimes a positive biopsy of the minor salivary glands. Usually one finds periartthritis in the ankle in sarcoidosis, but we did not observe periartthritis in our patients. We therefore suggest that the observation of uni- and bilateral ankle arthritis should be indicative of pSS, and thereby one of the differential diagnosis to be considered in ankle arthritis.

The frequency of arthritis in pSS in this study is significantly lower than reported for systemic lupus erythematosus (SLE) (14). SLE arthritis usually starts in the small joints of the hand (MCP and PIP joints) in a symmetrical fashion, and may be indistinguishable from early rheumatoid arthritis (15). SLE arthritis is less likely to be erosive, but can lead to deformities such as subluxations. The arthritis pattern we have described for pSS is therefore not directly comparable to SLE, with the main difference being the high frequency of ankle arthritis and lack of deformities in pSS.

Resolving non-destructive arthritis in finger joints, wrists, elbows, knees and ankles are usually reported in various viral diseases, and so is the lack of re-

Table I. Clinical and immunological characteristics of 102 patients participating in the study.

Age at diagnosis	53.4 years (range 19-78)
Sex	Female: male = 95:7
Positive lip biopsy focus score ≥ 1 per 4 mm ²	62/91 (68.1%)
Anti-SSA/SSB	34/102 (33.3%)
Rheumatoid factor IgM	41/102 (40.2%)
Rheumatoid factor IgA	25/97 (25.8%)
Anti-CCP	5/102 (4.9%)
ANA	81/102 (79.4%)
High serum IgG ≥ 15.3 g/liter	40/102 (39.2%)
Swollen salivary glands observed by rheumatologist	53/102 (52.0%)
or reported by patient	
Arthralgia	75/102 (73.5%)
Arthritis	18/102 (17.6%)

Table II. The pattern of arthritis in various joints in 18 patients with pSS, and results of analyzing anti-CCP and Rheumatoid factor RF-IgM and RF-IgA.

Patient	MCP	PIP	Wrist	Elbow	Shoulder	Knee	Ankle	MTP	RF factor IgM IgA	Anti-CCP
A	Yes	Yes	Yes**						Neg -	Neg
B					Yes				Pos Pos	Neg
C							Yes	Yes	Pos Pos	Neg
D	Yes**	Yes	Yes	Yes	Yes				Pos Neg	Neg
E	Yes**						Yes**	Yes	Pos Pos	Neg
F				Yes					Pos Pos	Neg
G*	Yes							Yes	Neg Neg	Neg
H					Yes				Neg Neg	Neg
I								Yes	Neg Neg	Neg
J	Yes		Yes**						Neg Neg	Pos
K		Yes	Yes						Neg Neg	Neg
L*							Yes**		Neg Neg	Neg
M					Yes		Yes	Yes	Neg Neg	Neg
N*					Yes**		Yes**		Neg Neg	Neg
O						Yes			Neg Neg	Neg
P*						Yes	Yes**		Pos -	Neg
Q							Yes		Pos -	Neg
R*	Yes	Yes	Yes**		Yes			Yes	Neg	Pos
TOTAL	6	4	5	2	6	2	7	6		

*Observed arthritis at more than one clinical examination.

**Bilateral.

action of acute phase reactants such as ESR and CRP in arthritis. Retrovirus may be associated with arthritis in knees, ankles, wrists, and occasionally small finger joints, while infection with Epstein-Barr virus may be associated with monoarticular arthritis in the knee (16). Both of these viruses have been associated with the pathogenesis of pSS, although the evidence for this is circumferential.

Primary Sjögren's syndrome is an autoimmune disorder where immunological mechanisms are of pathogenic importance and closely associated with clinical manifestations. Extraglandular disease manifestations in pSS have been described in association with immunological findings such as the plasma level of immunoglobulin IgG (4) and the presence of the autoantibodies anti-SSA/SSB (3, 5). The lack of an as-

sociation between arthritis and any of the immunological factors tested such as anti-SSA/SSB, IgG and IgA rheumatoid factor, anti-CCP, ANA, plasma immunoglobulin IgG and positive lip biopsy in the present study might therefore be indicative of a non-immunological mechanism for arthritis and arthralgia in pSS. In the present study we found that the presence of anti-cyclic citrullinated peptides were uncommon

in pSS, in accordance with other studies (17).

The preliminary European Classification criteria for pSS used in the present study has been criticized for including patients without immunological disease. We have therefore also applied the same calculations performed in the present study on the same population of patients diagnosed according to the proposed USA-European classification criteria (18). The number of included patients is thereby reduced from 102 til 67, but the results did not change significantly.

As a conclusion, arthritis in pSS is less common than in SLE, and is usually mild, resolving, and unrelated to other clinical and immunological factors. The arthritis pattern is more like the pattern found in retrovirus infections than in other inflammatory rheumatic diseases. It calls for a study performing ultrasonography on joints in hands of patients with pSS.

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