Clinical follow up study of 87 patients with sicca symptoms (dryness of eyes or mouth, or both)

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Abstract

Objective—To assess the prognosis of patients with sicca symptoms and to identify the clinical and immunological factors that most sensitively predict the later development of primary Sjögren's syndrome (SS) or other connective tissue diseases.

Methods—Eighty seven patients (72 female, 15 male) with sicca symptoms were re-evaluated after a median follow up time of 11 years (range 8–17). The clinical examination included ophthalmological examination (Schirmer's test, break up time and Rose-Bengal staining). Labial salivary gland biopsy was performed and histological findings graded according to the Chisholm-Mason scale. The immunoserological tests included determination of rheumatoid factor (RF), antinuclear antibodies (ANA), anti-extractable nuclear antigen-antibodies (ENA), serum immunoglobulins IgA, IgG, and IgM, and serum β_2 -microglobulin (β_2m).

Results—At follow up 31 patients (36%) fulfilled modified Californian criteria (salivary flow measurements were not performed and Chisholm-Mason grades 3–4 were regarded as diagnostic histological findings) for possible or definite SS. Likewise, a significant progression of the histological findings was observed. Labial salivary gland re-biopsy was performed in 42 patients with grade 0–2 findings at baseline, progression to grades 3–4 being observed in 21 (50%) at follow up. The patients who later developed SS were at baseline significantly older (mean (SD) 52 (9) v 44 (14) years, $p \leq 0.005$) compared with those not fulfilling the SS criteria at follow up; they also had significantly higher serum β_2m ($p \leq 0.0005$) and IgG concentrations ($p \leq 0.005$), and they had positive ANA more frequently ($p \leq 0.01$).

Conclusion—These results suggest that high age, increased values of serum β_2m , ANA positivity and increased concentrations of serum IgG, might be useful indicators for the subsequent development of SS in patients with sicca symptoms. The prognosis of patients with these symptoms was favourable, and the clinical course was benign even in the 36% of patients who developed SS. No cases of lymphoma were observed.

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Sjögren's syndrome (SS) is a chronic autoimmune exocrinopathy characterised by dryness of eyes (keratoconjunctivitis sicca) and mouth (xerostomia) as well as recurrent parotid or submandibular gland swellings. The clinical course of SS has been regarded as chronic, mild and stable. However, apart from the effects on the lacrimal and salivary glands, various extraglandular manifestations may develop. Also, an increased risk of lymphoproliferative diseases, especially of non-Hodgkin's lymphoma, has been related to SS.¹

Scant attention has been paid to the prognosis and progression of mild, smouldering diseases and sicca symptoms. Forstot *et al* made a study of 45 patients with keratoconjunctivitis sicca with respect to oral and serological findings and observed SS in eight (17%).² In a long term follow up study of 106 SS patients a subgroup of patients with isolated keratoconjunctivitis sicca was also described.³ None of the patients with isolated keratoconjunctivitis sicca developed lymphoproliferative disease.

Our study was specifically designed to evaluate the prognosis of SS in the mildest forms of its clinical spectrum and to obtain further information on the natural history of primary SS (pSS). The main purpose was to identify the most useful clinical and immunological indicators of the subsequent development of SS in patients with early onset sicca symptoms.

Methods

SELECTION OF SUBJECTS WITH SICCA SYMPTOMS FOR RE-EVALUATION

The charts of 259 subjects with sicca symptoms initially examined in the Department of Internal Medicine, Section of Rheumatology, in Tampere University Hospital during the years 1977 to 1986 were reviewed by one of the authors (MP). Californian criteria⁴ with the modifications that salivary flow rate measurements were not performed and the histological findings were graded according to the Chisholm-Mason scale⁵ grades 3 and 4 regarded as diagnostic, were applied in the diagnosis of SS. One hundred and nine patients with sicca symptoms fulfilling two or less of the criteria were included in the study. Of these, 14 subjects had died; the causes of death being cardiovascular in seven, malignancy in five, hepatic cirrhosis in one, and accident in one patient. The remaining 95 subjects were invited for re-evaluation. A total of 87 subjects (92% of those invited) attended the study. They comprised 72 women and 15 men with a median age of 60 years (range, 28–80) and a median follow up time of 11 years (range, 8–17).

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METHODS OF RE-EVALUATION

The clinical examination included a thorough interview covering family history, previous diseases, previous and concurrent medications, drug allergies, duration of sicca symptoms, first manifestation of the disease, existence of recurrent parotid or submandibular gland swellings, and present sicca symptoms of the eyes and mouth. The existence of xerostomia was defined as subjective troublesome daily feeling of dry mouth for more than three months. Special emphasis was focused on possible extraglandular symptoms (musculoskeletal, dermatological, renal, neurological, vascular, respiratory, gastrointestinal, endocrine and lymphoproliferative symptoms).

Rheumatoid factor (RF) was determined by Waaler-Rose agglutination test (at baseline) and by laser nephelometry (at follow up). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on multiblock cryostat sections, comprising rat liver and mouse kidney, heart and stomach (at baseline) and using Hep-2 cells (at follow up). Antibodies to extractable nuclear antigens (ENA), including anti-ribonucleoprotein (RNP), anti-Sm, anti-SS-A, anti-SS-B and anti-Scl 70 antibodies, as well as antibodies to native DNA (QUANTA Lite ENA 5 ELISA and QUANTA Lite ds DNA, INOVA Diagnostics Inc, San Diego, CA), were measured by enzyme immunoassay. Anti-salivary gland antibodies were analysed by indirect immunofluorescence (Monkey Salivary Gland Slide, INOVA Diagnostics Inc). Serum concentrations of immunoglobulin IgA, IgG and IgM, as well as serum complement levels (C3 and C4), were measured by laser nephelometry. Serum β_2 m was determined by radioimmunoassay (Pharmacia beta-2-micro RIA kit, Pharmacia Diagnostics Uppsala, Sweden, the reference values being 1.0–2.5 mg/l).

Ophthalmological examination was performed at baseline and at follow up (the latter by one senior ophthalmologist, HU). Tear fluid secretion ≤ 9 mm/5 min in Schirmer's test and break up time < 10 s were defined as abnormal test results. Rose-Bengal test was performed by the application of 1% solution of Rose-Bengal dye using a glass applicator and by evaluating abnormal staining at the interpalpebral area of the cornea and conjunctiva using a slit lamp. Keratoconjunctivitis sicca was established if diagnostic criteria (decreased Schirmer test result and abnormal staining in Rose-Bengal test) were met in at least one eye.

Labial salivary gland biopsy was performed at baseline in 73 of the 87 patients and the histological findings were graded according to the Chisholm-Mason scale (grades 0–4).⁵ At follow up labial biopsy was repeated for those patients who had grade 0–2 histological findings initially and who gave their informed consent. A thorough otorhinolaryngological examination was made and follow up labial salivary gland biopsy samples through lower lip mucosal incision were taken by a senior otorhinolaryngologist (JP). The histological evaluation was made blind to the clinical data by an experienced pathologist (HH). The study

design was approved by the Ethical Committee of Tampere University Hospital.

STATISTICAL ANALYSIS

To evaluate differences between the patient groups, Student's *t* test and χ^2 test with Yates's correction were used for continuous and dichotomous variables, respectively. Logistic regression analysis was applied to evaluate the independent effect of different laboratory findings on the prognosis of the disease.

Results

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENT GROUPS AND THE SICCA AND XEROSTOMIA SYMPTOMS

At follow up 31 patients (26 women, 5 men) out of 87 (36%) fulfilled modified Californian criteria for possible (22 patients) or definite (9 patients) SS (referred to as the SS group). Twenty nine of these patients had primary and two had secondary SS to either rheumatoid arthritis or mixed connective tissue disease (MCTD). In the patient group not fulfilling the criteria for SS (referred to as the sicca group) two patients fulfilled the criteria for rheumatoid arthritis and one had undifferentiated connective tissue disease (UCTD) at follow up. Furthermore, three patients in the sicca group had features of a seronegative spondylarthropathy and two of a non-specified oligoarthritis. The sicca group comprised 56 patients (46 women, 10 men).

Patients in the SS group were significantly older than those in the sicca group (mean (SD) 63 (8) *v* 55 (13) years at follow up, $p \leq 0.005$). The duration of xerostomia was significantly longer in the SS group compared with the sicca group (13 (7) *v* 10 (7) years, $p \leq 0.05$); but the difference in the duration of sicca symptoms in the eyes between the SS and sicca groups (13 (10) and 11 (7) years, respectively) was not statistically significant.

Sicca symptoms of the eyes did not occur as frequently at baseline in the SS group (61%) as in the sicca group (84%). Both xerostomia and a history of either parotid or submandibular gland swelling were found at baseline more frequently in the SS group (77% and 32%, respectively) compared with the sicca group (63% and 20%, respectively). Neither of the differences was statistically significant. There were no statistically significant differences in previous or concurrent use of diuretics, β blockers, psychiatric medication, tear and salivary substitutes, corticosteroids or disease modifying antirheumatic drugs between the patient groups.

OPHTHALMOLOGICAL FINDINGS

Table 1 describes the ophthalmological findings. At baseline 53% of the patients in the SS group and 57% of those in the sicca group had abnormal results in Schirmer's test. Abnormal staining in Rose-Bengal test was constituted at baseline in 56% and 40% of the patients in SS and sicca groups, respectively. The criteria of keratoconjunctivitis sicca were fulfilled on the whole in 32% of the patients in both groups at baseline.

Table 1 Ophthalmological findings

Test	Patients with sicca symptoms		Patients who developed SS	
	Baseline	Follow up	Baseline	Follow up
Schirmer test result ≤ 9 mm	32/56 (57)	24/56 (43)	16/30 (53)	22/31 (71)
Break up time < 10 s	10/33 (30)	8/54 (15)	7/19 (37)	10/30 (33)
Increased staining in Rose-Bengal test	21/52 (40)	22/56 (39)	15/27 (56)	25/31 (81)
Criteria for KCS fulfilled	18 (32)	17 (30)	10 (32)	24 (77)

SS = Sjögren's syndrome; KCS = Keratoconjunctivitis sicca. Percentages shown in parentheses.

LABIAL SALIVARY GLAND BIOPSY SPECIMENS

New labial salivary gland biopsy specimens were taken from 55 patients, and 50 of these were representative (containing more than four minor salivary glands/4 mm²). The biopsy was not performed in 11 patients with grade 3 or 4 findings already at baseline. Twenty one were reluctant to undergo re-biopsy. Evaluable baseline and second labial salivary gland biopsy specimens were available from 42 patients. Of the 42 labial salivary gland re-biopsies of patients with grade 0–2 findings at baseline, progression to grades 3–4 was observed in 21 (50%) at follow up (table 2); of those, altogether 12 specimens progressed from grade 0–2 up to grade 4—that is, to a finding of two or more lymphocytic foci. The histological progression extended to at least two grades in 17 (40%) of these specimens—two grades in nine biopsy specimens, three grades in seven and four grades in one biopsy specimen—as compared with the baseline specimens.

Table 2 Histological findings in labial salivary gland biopsy specimens

Grade*	Number of patients at baseline (%)	Number of patients at follow up (%)
0	16 (22)	16 (32)
1	29 (40)	7 (14)
2	17 (23)	5 (10)
3	8 (11)	9 (18)
4	3 (4)	13 (26)
Total	73 (100)	50 (100)

*The histological findings were graded according to the Chisholm-Mason scale.⁵

Table 3 Immunological findings in the patient groups at baseline and at follow up

Variable	Patients with sicca symptoms (n=56)		Patients who developed SS (n=31)	
	Baseline	Follow up	Baseline	Follow up
Number of patients positive for				
Waalser-Rose	9/55 (16%)		4/31 (13%)	
fs-RF		11/56 (20%)		10/31 (32%)
ANA-ab	2/56 (3%)	9/56 (16%)	8/31 (26%)*	18/31 (58%)
DNA-ab	0/48	7/56 (12%)	2/29 (7%)	6/31 (19%)
ENA-ab				
RNP		2 (4%)		2/30 (7%)
Sm		1 (2%)		2/30 (7%)
SS-A-ab		3/56 (5%)		12/30 (40%)
SS-B-ab		2/56 (4%)		10/30 (33%)
Scl70		0/11		1/8 (13%)
Salivary gland antibodies		8/56 (14%)		1/31 (3%)
S-IgA (g/l)	2.18 (0.93)	2.36 (1.09)	2.46 (1.19)	2.93 (2.10)
S-IgG (g/l)	12.9 (4.4)	12.7 (3.8)	16.6 (7.1)**	15.2 (4.8)
S-IgM (g/l)	1.60 (1.43)	1.72 (2.02)	1.41 (0.80)	1.45 (0.76)
S- γ globulin (g/l)	11.8 (3.6) (n=50)		15.1 (7.3)** (n=28)	
S- β_2 m (mg/l)	1.63 (0.50)	1.78 (0.73)	2.15 (0.56)***	2.43 (1.46)

The baseline concentrations were compared with Student's *t* test and the occurrence of autoantibodies at baseline was compared with χ^2 test. Significances: **p* $\leq$ 0.01, ***p* $\leq$ 0.005, ****p* $\leq$ 0.0005. RF = Rheumatoid factor; ANA-ab = antinuclear antibodies; DNA-ab = antibodies to double-stranded DNA; ENA-ab = antibodies to extractable nuclear antigen; S- β_2 m = serum β_2 -microglobulin. Data shown as mean (SD) and percentages.

EXTRAGLANDULAR MANIFESTATIONS

At follow up there were no significant differences between the patient groups in the frequency of arthralgias or arthritis. Erosive arthritis was detected in only one patient in the SS group, and in two patients in the sicca group; all the patients with erosive arthritis had also rheumatoid arthritis. The frequencies of Raynaud's phenomenon, peripheral or central nervous system symptoms between the patient groups did not differ. Myositis was not found. Pleuritis had occurred in six (19%) of the patients in the SS group and in two (4%) subjects in the sicca group but its relation to SS can retrospectively not be assured. Pericarditis had appeared in no patient in the SS group and in two (4%) patients in the sicca group. In the SS group two patients (6%) had pulmonary fibrosis and one patient (3%) had lymphocytic interstitial pneumonitis. Furthermore, one patient (3%) in the SS group had a biopsy confirmed interstitial nephritis. In the sicca group four patients had developed breast cancer, but in the SS group no malignancies occurred.

STANDARD LABORATORY TESTS

There were no significant differences between the patient groups in blood haemoglobin concentration, serum white blood cell count, serum platelet count, serum C reactive protein, serum creatinine, serum alanine aminotransferase or serum alkaline phosphatase at baseline or at follow up. The patients in the SS group had significantly higher erythrocyte sedimentation rate (ESR) at baseline compared with the sicca group (mean (SD) 29 (25) *v* 20 (19), *p* $\leq$ 0.05).

IMMUNOSEROLOGICAL TESTS

There were no differences between the patient groups in the frequency of positive results in the Waaler-Rose test at baseline (table 3). The SS group had ANA more frequently at baseline than the sicca group (26% *v* 3%, *p* $\leq$ 0.01). ENA antibody determinations were available comprehensively only at follow up; the occurrence of SS-A and SS-B antibodies was significantly higher among the SS patients than in the sicca group (40% *v* 5%, *p* $\leq$ 0.001 and 33% *v* 4%, *p* $\leq$ 0.001, respectively) (table 3). There were no significant differences in the levels of serum complement components (C3 and C4) between the patient groups at baseline. The concentrations of serum γ globulin and serum IgG as well as the level of serum β_2 m were significantly higher in the SS group than in the sicca group at baseline (table 3).

LOGISTIC REGRESSION ANALYSIS

As several of the clinical and laboratory findings were likely to be intercorrelated, a logistic regression analysis was performed to assess their independent impact on disease outcome. The effect of ESR was found to be dependent on age, but the significance of the other parameters tested (ANA positivity, serum γ globulin, serum IgG, serum β_2 m) was found to prevail irrespective of the effect of age as predictors of later development of SS (table 4). Age, ESR, ANA positivity, serum γ globulin

Table 4 Summary of results of logistic regression analysis

Dependent variable	Independent variables	OR	95 % CI	p value
Development of Sjögren's syndrome	Age	1.0932	1.04, 1.15	0.0009
	ANA positivity	32.5143	4.33, 244.29	0.0007
Development of Sjögren's syndrome	Age	1.0620	1.01, 1.11	0.0142
	Serum γ globulin	1.1637	1.02, 1.32	0.0219
Development of Sjögren's syndrome	Age	1.0600	1.01, 1.11	0.0185
	Serum IgG	1.1447	1.03, 1.27	0.0104
Development of Sjögren's syndrome	Age	1.0677	1.01, 1.12	0.0119
	Serum β_2 m	6.4573	1.98, 21.01	0.0019
Development of Sjögren's syndrome	Age	1.0534	1.01, 1.10	0.0212
	ESR	1.0097	0.99, 1.03	0.4045
Development of Sjögren's syndrome	Age	1.0837	1.02, 1.16	0.0150
	ANA positivity	25.0425	2.15, 292.10	0.0102
	Serum β_2 m	5.9752	1.30, 27.37	0.0213

OR = Odds ratio; CI = confidence intervals; ANA-ab = antinuclear antibodies; S- β_2 m = serum β_2 -microglobulin; ESR = erythrocyte sedimentation rate.

and IgG concentrations as well as serum β_2 m levels were also tested all together in a logistic regression model in a backward stepwise manner to eliminate intercorrelation of these parameters. Age, ANA positivity and serum β_2 m were found to be independent predictive factors for the development of SS in subjects with sicca symptoms (table 4).

Discussion

Our main result was, that 31 of 87 subjects (36%) with either complaints of dryness of eyes or mouth, or both, developed SS after a median follow up time of 11 years. Factors that could predict the development of clinical SS were: higher age, positive antinuclear antibodies, increased concentrations of serum γ globulin and serum IgG as well as a high concentration of serum β_2 m. Furthermore, our results showed that there was a significant progression in the histological findings in labial salivary gland specimens in the course of time. No cases of lymphoma were found.

The proportion of the patients who finally developed clinically evident SS (approximately one third of the group) seems to be fairly small considering the length of the follow up (median 11 years). This implies that the development of SS is probably a particularly slow process. We had modified the Californian criteria,⁴ and regarded as diagnostic histological findings those with at least one lymphocytic focus. If we had adhered strictly to the Californian criteria necessitating more than one lymphocytic focus to be found to establish the diagnosis, the proportion of patients having developed SS would naturally have been even smaller. In previous studies, even lower frequencies of SS among patients with sicca or xerostomia symptoms have been noted. In an earlier prospective study among 45 patients with keratoconjunctivitis sicca, xerostomia was observed in 15 patients (33%) but complete SS in only eight (17%).² Markusse *et al*⁶ found that only 20% of patients (10 of 50) with eventual SS were diagnosed at their first rheumatological visit, and the diagnostic delay was on the average three years. In a retrospective study of 47 patients with pSS, it was noted that an average of eight years had elapsed before the diagnosis was made.⁷ In a prospective study on sicca symptoms of six patients with primary and nine with secondary SS it was shown that both subjective sicca symptoms and objective findings of glandular

involvement progress, although very slowly, and that three patients with subclinical disease developed clinical SS in six years.⁸ In another study, none of 56 patients with isolated keratoconjunctivitis sicca was reported to have developed SS at follow up 10–12 years after the initial diagnosis.³ In that study, however, the follow up assessment did not include a second labial salivary gland biopsy.³

It might be argued that had we applied the EEC criteria⁹ instead of the Californian⁴ in diagnosing SS, some of our patients with sicca symptoms would have fulfilled the criteria already at baseline. However, in that case these subjects would have been excluded from the study, and correspondingly the percentual proportion of the patients fulfilling the diagnostic criteria at follow up would thus not necessarily differ from the current results.

In our study there was no progression in the ophthalmological findings in the sicca group during the follow up. This is in accordance with results of an earlier study¹⁰ where the course of keratoconjunctivitis sicca was evaluated. It was found that the Schirmer test results remained unchanged and the average ocular findings evaluated by break up time and Rose-Bengal tests improved during the mean follow up period of 53 months.¹⁰ Also in the study by Kruize *et al*,³ the proportion of patients with keratoconjunctivitis sicca having inflammatory reaction of eyes, was lower at follow up than at baseline. In our study, however, progression of the ocular findings was observed in the SS group (table 2).

There was a significant progression of histological findings in this study. Serial assessments of histological findings have been described in patients with SS.^{11, 12} In these studies also, the lesions were mainly progressive with time. Leroy *et al*¹¹ report that even eight of the nine initially negative analyses were positive on the second sample. Jonsson *et al*¹² observed morphological progression of sialadenitis in 14 of 21 patients (67%) with primary SS, and in 14 of 18 patients (78%) with secondary SS after a mean (SD) follow up time of 39 (20) months.

Martinez-Lavin *et al*¹³ found that identification of SS-A and SS-B antibodies helped for establishing the findings of SS in patients in whom the diagnosis had not been considered at the initial examination. The prognostic value of SS-A antibodies has been confirmed by others.¹⁴ Otherwise, no predictive factors for SS development have previously been suggested. In a large follow up material of Kruize *et al*³ involving both SS patients (31 primary and 19 secondary) and keratoconjunctivitis sicca patients (56) it was sought to find laboratory factors predictive of the development of extraglandular symptoms of SS, but no such factors were found.

In our study higher age at onset, ANA positivity and high serum serum β_2 m levels attained statistical significance and proved to be independent predictive factors for the later development of SS also in a logistic regression model. Previously, high serum β_2 m values have been reported especially in SS patients with lymphoproliferative complications or renal

involvement.¹⁵ It is noteworthy that in our study SS-A and SS-B antibodies were not included in the analysis of predictive factors because of the fact that the earliest baseline examinations were performed already in the 1970s when SS-A and SS-B antibody determinations were not available in clinical practice.

No patients with lymphoma were recorded in our study. The increased risk of lymphoma in SS has previously been described in several studies.^{1, 3, 16, 17} Our study was focused on a population in which the diagnosis of SS was not yet established in the first evaluation, and thus the observation period was probably shorter than in populations where the diagnosis of SS is already apparent. In a recent follow up study (median 34 months) of 100 patients with primary SS, lymphoma was found in excess (three patients).¹⁸

In conclusion, our results suggest that higher age, increased concentrations of serum β_2 m, ANA positivity and, to a lesser extent, high concentrations of serum γ globulin and serum IgG, might be useful indicators for the subsequent development of SS in patients with sicca symptoms. There was a significant progression in the histological findings in labial salivary gland biopsies over time, and it might thus be justified to take a new labial salivary gland biopsy specimen after some years to confirm the diagnosis of SS in cases where the first specimen has proved negative in patients with persisting symptoms and indicators suggestive of SS. In our study the prognosis of patients with sicca symptoms was favourable and the clinical course was benign even in those patients who developed SS. No cases of lymphoma were observed.

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