Clinical and Immunological Factors Associated with Low Lacrimal and Salivary Flow Rate in Patients with Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** To study which clinical and immunological factors may be associated with low salivary and lacrimal flow in patients with primary Sjögren's syndrome (SS). Are the lacrimal and salivary flows influenced by age of the patient, age at diagnosis, disease duration, or findings in the biopsies of the minor salivary glands, or are immunological factors of importance for reduced flow rates?

Methods. In total 72 patients (mean age 57 yrs and disease duration 13.5 yrs) with primary SS diagnosed according to the European classification criteria were evaluated objectively by serological testing and by measures of exocrine gland function, such as unstimulated whole saliva collection (UWSC) and by Schirmer I test.

Results. Salivary flow (UWSC) in 72 patients with primary SS correlated to the presence of antinuclear antibodies (ANA) ($r = -0.32$, $p = 0.006$) and to anti-SSA/SSB ($r = -0.31$, $p = 0.010$). No such correlation was seen for the lacrimal flow, and there was no mutual correlation between lacrimal and salivary flow. UWSC was significantly lower in patients with anti-SSA versus those without anti-SSA (1.63 ml vs 2.63 ml; $p < 0.007$), while such a significant difference was not observed in the presence versus absence of anti-SSB. The salivary and lacrimal flow was not significantly affected by age of the patient, and did not correlate to age at diagnosis, sex, disease duration, rheumatoid factor finding, or findings in minor salivary gland biopsies.

Conclusion. Salivary flow in patients with primary SS was negatively correlated with immunological factors such as ANA and anti-SSA/SSB, in contrast to low lacrimal flow, where no such correlation was seen. There was no association of lacrimal and salivary flow with age of patient, age at diagnosis, disease duration, and findings in minor salivary gland biopsies. The results indicate that reduced salivary flow is closely associated with immunological factors, and is not associated with the age of the patient or infiltration of lymphocytes in salivary glands. (J Rheumatol 2002;29:305–8)

Key Indexing Terms:
PRIMARY SJÖGREN'S SYNDROME SALIVA TEARS ANTINUCLEAR ANTIBODIES

Primary Sjögren's syndrome (SS) is a chronic autoimmune rheumatic disorder of unknown etiology mainly affecting salivary and lacrimal glands. The disorder is characterized clinically by dry eyes and dry mouth[1,2], the hallmarks of SS. The disease is systemic, however, expressing a diverse clinical spectrum extending from an organ-specific autoimmune exocrinopathy to a systemic disorder affecting several organs.

Oral and ocular dryness is caused by a substantial decrease in the flow of saliva and tears, and the decrease in flow is traditionally thought to be due to a progressive replacement of the parenchyma of the exocrine glands by a lymphocytic infiltrate. Recent studies in animal models have challenged this view, however, claiming that lacrimation and salivation are not related to lymphocytic infiltration in lacrimal and salivary glands[3]. Based on animal studies, it has also been shown that the secretory dysfunction is mediated by antimuscarinic acetylcholine receptor antibody[4]. These findings, indicating that immunological factors are associated with secretory dysfunction, have been supported by a study of 16 patients with primary SS showing that the autoantibodies anti-SSA/SSB were correlated to the salivary flow[5].

The purpose of this study was to evaluate the association of various clinical and immunological factors with reduced lacrimal and saliva flow in 72 patients with primary SS.

MATERIALS AND METHODS

From 1992 to 1997 patients with primary SS in the Bergen area of Norway were prospectively and consecutively registered at Haukeland University Hospital. Patients were diagnosed according to the classification criteria proposed by The European Classification Criteria Group in 1996[6]. Registered patients with SS are examined once yearly, and in addition to a physical and biochemical examination, they go through a structured interview screening for the presence of disease manifestations.

Onset of the disease was defined as the first subjective experience of symptoms of any of the items in the European criteria[6] or arthritis/arthralgia, elevated long standing erythrocyte sedimentation rate (ESR) without any obvious cause, peripheral neuropathy, long standing fever without infection, or excessive chronic fatigue leading to examination by the patient's doctor.

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Supported by The Aslaug Andersen Foundation.

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Submitted January 10, 2001; revision accepted August 17, 2001.

Arthritis was defined as swollen and tender joints observed by the examining doctor. Disease duration was defined as the time from onset to examination for this study. Patients taking anticholinergic drugs and diuretics were excluded from the study.

The study included 65 women and 7 men with primary SS. The mean age (range) and duration of disease (time from onset) at the time of the study were 57 years (25–79) and 13.5 years (1.8–51.8), respectively. The mean age at onset and at diagnosis were 43.2 (14–68) and 53.2 years (19–77), respectively.

Diagnostic methods. A biopsy from the minor salivary glands of the lower lip had been performed in 67 (93.1%) patients at the time of diagnosis, and the biopsy was evaluated with focus scoring according to the method described by Greenspan, *et al*[7]. A biopsy with focus score > 1 per 4 mm^2 was considered positive. Lacrimal flow rate and salivary flow rate were evaluated by Schirmer I test and unstimulated whole saliva collection (UWSC) as described[8]. Schirmer I test was considered positive when the wetting was < 5 mm/5 min. UWSC was considered positive when < 1.5 ml whole saliva was collected in 15 min.

Laboratory analysis. Antinuclear antibodies (ANA), rheumatoid factor (RF), antibodies against SSA and SSB, and immunoglobulin G in serum (s-IgG) were analyzed as described[8,9].

Statistical analysis. Correlations between clinical and laboratory variables were calculated by means of Pearson's correlation coefficient and Spearman's rank correlation coefficient. Analysis comparing groups of variables was performed using chi-square test, Student t test, Mann-Whitney U test and one-way ANOVA test, as well as Kruskal-Wallis test. P values < 0.05 were regarded as statistically significant.

RESULTS

Positive biopsy of the minor salivary glands with focus score > 1 per 4 mm^2 was observed in 49 of 67 patients (73.1%). Positive ANA was found in 55 patients (76.4%), positive anti-SSA and/or SSB in 26 (36.1%), positive RF in 32 (44.4%), and high s-IgG in 29 patients (40.3%).

Low salivary flow rate was observed in 38 patients (52.8%). Low lacrimal flow rate measured by Schirmer I test for one eye only was found in 55 patients (76.4%), and for both eyes in 41 patients (56.9%).

As shown in Table 1, the unstimulatory salivary flow rate UWSC was not significantly different in the various age groups of patients. The relative number of patients with reduced salivary flow or reduced lacrimal flow measured by Schirmer I test in both eyes or one eye was not significantly influenced by age.

By correlation analysis the unstimulated salivary flow rate UWSC was correlated to the presence of anti-SSA/anti-SSB ($r = –0.31$, $p = 0.010$) and to ANA ($r = –0.32$, $p = 0.006$) in serum, but no correlation to Schirmer I test in both eyes or one eye was found. UWSC was not correlated to disease duration ($r = –0.053$, $p = 0.67$), age at diagnosis, age at first symptoms, sex, RF, positive focus score in biopsies from the small salivary glands, or high serum IgG.

Lacrimal flow rate in one or both eyes by the Schirmer I test was not correlated to ANA, anti-SSA/SSB, RF, UWSC, disease duration, sex, age at diagnosis or age at first symptom of primary SS, high level of IgG in serum, or focus score in lower lip minor salivary gland biopsy.

Comparing patients with low versus normal unstimulated salivary flow rate (Table 2), positive ANA was found in 86.8% versus 64.7% ($p = 0.026$), 47.4% had positive anti-SSA and/or anti-SSB versus 23.5% ($p = 0.031$), and 52.6% had high serum IgG versus 26.5% ($p = 0.021$), respectively. There was no significant difference between these 2 groups of patients regarding the presence of RF, positive biopsy of the minor salivary glands, and episodes of swollen salivary glands reported by the patients or revealed by clinical examination.

Identical analysis comparing patients with low versus normal Schirmer I test in both or only one eye did not reveal any significant difference between groups (data not shown).

Comparing patients with low versus normal unstimulated salivary flow rate, positive Schirmer I test in both eyes was observed in 57.5% versus 42.5% (NS), and in only one eye in 54.5% versus 45.5% (NS).

As shown in Table 3, the mean salivary flow was significantly lower in patients with the presence of ANA or anti-SSA versus those without such autoantibodies. No such significant difference in salivary flow was noted in patients with versus those without anti-SSB, RF, high serum level of IgG, and positive biopsy of the minor salivary glands (data not shown).

DISCUSSION

It is well known that measurement of lacrimal and salivary flow may show variations in the same individual over time. Saliva, which is produced by 3 major and numerous minor salivary glands, exhibits great flow variations among healthy individuals and in the same individual under diverse conditions[10,11], and salivary flow measurements could therefore be potentially unreliable. In Sjögren's syndrome, however, we have found that measurements of lacrimal and salivary flows are generally stable and reliable when performed under standardized conditions[8]. In addition, the Schirmer I test and UWSC have acceptable sensitivity and specificity to be included in classification criteria for SS[6].

In this study the unstimulated salivary flow rate UWSC correlated to the presence of ANA and anti-SSA/SSB, but not to focus score in biopsies from the small salivary glands and not to disease duration. The lacrimal flow was not correlated to any of these immunological factors, however, and we found no mutual correlation between the lacrimal and salivary flow. It has recently been reported that in patients with rheumatoid arthritis and sicca symptoms, there is a weak correlation between Schirmer I test and unstimulated whole saliva collection[12]. It is not surprising that items in classification criteria are mutually correlated, but in the present study UWSC was used in the diagnostic procedure in only 22 of the 72 patients, thereby making this bias less likely.

The traditional view is that lymphocytic infiltration of the exocrine glands causes the dysfunction of the glands. As the lymphocytic infiltration progresses over time[13], one would therefore expect a gradual decline of glandular function. In this study, however, we could not observe any association between low lacrimal and saliva flow and positive biopsy of

Table 1. Lacrimal and salivary flow in various age groups of patients with primary Sjögren's syndrome. Low lacrimal flow rate as measured by Schirmer I is ≤ 5 mm/5 min, while low salivary flow measured by unstimulated salivary flow rate is ≤ 1.5 ml/15 min.

	20–39 yrs, N = 7	40–49 yrs, N = 16	50–59 yrs, N = 18	60–69 yrs, N = 15	70–89 yrs, N = 16	p*
Unstimulated salivary flow rate, ml/15 min	1.29	2.04	3.19	2.41	1.84	NS
Patients with low salivary flow rate	5/7	8/16	7/18	6/15	13/16	NS
Patients with low Schirmer I, both eyes	4/7	5/16	10/18	11/15	11/16	NS
Patients with low Schirmer I, one eye	5/7	10/16	15/18	12/15	13/16	NS

* For significance of difference between groups. p ≤ 0.05 by one-way ANOVA and Kruskal-Wallis test.

Table 2. Presence of autoantibodies, high serum IgG, and positive biopsy of minor salivary glands in 72 patients with primary SS with normal and low unstimulated salivary flow rate.

	Patients with Low Unstimulated Salivary Flow Rate, n = 38	Patients with Normal Unstimulated Salivary Flow Rate, n = 34	p*
Positive ANA	33/38	22/34	0.026
Positive RF	20/38	12/34	NS
Positive anti-SSA/SSB	18/38	8/34	0.031
High serum IgG	20/38	9/34	0.021
Positive biopsy of minor salivary glands, focus score ≥ 1	29/35	2/32	NS
Swollen salivary glands**	20/38	16/34	NS

* For significance of difference p ≤ 0.05 by chi-square test.
** Self-reported or observed by clinical examination.

Table 3. Mean salivary flow given as ml/15 min in patients with and without the presence of the autoantibodies ANA, anti-SSA, and anti-SSB.

Positive ANA	Negative ANA	p	Positive Anti-SSA	Negative Anti-SSA	p	Positive Anti-SSB	Negative Anti-SSB	p*
2.10	2.88	0.007	1.63	2.63	0.007	2.06	2.37	NS (0.28)

* Mann-Whitney U test.

the minor salivary glands with focus scoring, and there was no association with duration of disease. The lack of association with focus scoring in biopsies is in disagreement with 2 studies[5,14] that described correlation between salivary flow and labial salivary gland focus score. The first study included only 16 patients[5], and the second study used other classification criteria and stimulated instead of unstimulated salivary flow collection — making the results not comparable with the present study. On the other hand the results of the present study support the finding in animal models that there is no association between lymphocytic infiltration in exocrine glands and lacrimal and saliva flow[3].

It is interesting that UWSC was significantly lower in patients with versus those without anti-SSA autoantibodies, while this significant difference was not observed for the presence versus absence of anti-SSB. This observation may be biased by the low number of patients with anti-SSB autoantibodies.

It is well known that xerostomia is common in the elderly, but studies have determined that salivary gland function is well preserved in the healthy geriatric population[15,16]. Therefore, dry mouth is probably not a condition of aging, but most likely of systemic or extrinsic origin. In this study there was no significant difference between lacrimal and saliva flow in the various age groups, indicating that measurements of lacrimal and saliva flow as a diagnostic tool in SS with the present cutoff values probably are valid in all age groups. The same observation was reported in patients with rheumatoid

arthritis with sicca symptoms[12]. The results in the present study also illustrate that there is no significant decline in exocrine gland function over time, making it less likely that lymphocytic infiltration causes the glandular dysfunction.

This study indicates that immunological factors are associated with low salivary flow in primary Sjögren's syndrome. Several autoantibodies have been suggested to be of pathogenic importance for the development of SS[1,2]. The most exciting development in this field is the evidence of antimuscarinic acetylcholine receptor antibody mediated secretory dysfunction in nod mice[4]. It has also recently been found that the acinar cells of patients with primary SS do possess a functional receptor system[17]. This gives a new perspective to the pathogenesis and hopefully also the treatment of a disorder that is one of the most common inflammatory rheumatic diseases[1,2].

ACKNOWLEDGMENT

I am grateful for the help of Dr. Tore Rygh, who contributed to the registration of these patients in 1992, and the help of the Department of Immunology and Microbiology, Haukeland University Hospital, in doing the serological analysis. Colleagues at the Broegelmann Research Laboratory have contributed to fruithful discussion about immunological aspects of Sjögren's syndrome. I am also grateful for the help of the clinical and laboratory staff at the Department of Rheumatology, Haukeland University Hospital. Finally, I highly appreciate the patients who participated in the study.

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