Fatigue and health profile in sicca syndrome of Sjögren's and non-Sjögren's syndrome origin

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ABSTRACT

Objective

To assess the health status and fatigue in sicca patients with or without Sjögren's syndrome (SS) and to test whether the immune-inflammatory activity or the extent of the disease predict fatigue in SS.

Methods

The Medical Outcomes Study Short-Form General Health Survey (MOS SF-36) was used in 1° SS (n = 90), 2° SS (n = 24), non-SS patients with sicca symptoms (n = 15) and healthy population controls (n = 126). Laboratory values and clinical findings were used to predict fatigue in SS.

Results

74% of the SS and 80% of the non-SS sicca patients felt themselves tired. Vitality score values were 40.2 ± 20.3 in 1° SS, 42.1 ± 20.6 in 2° SS and 29.0 ± 15.8 in non-SS. The health profiles were similar in 1° and 2° SS, worse ($p < 0.001$) than in normal controls, but in most aspects better than in non-SS sicca patients. In SS neither hemoglobin, ESR nor CRP predicted fatigue. Surprisingly, high serum IgG ($p < 0.05$), antinuclear antibodies (ANA) ($p < 0.01$) and SS-A antibodies ($p < 0.05$) values correlated positively with vitality. The number of disease manifestations correlated negatively with vitality ($p < 0.004$). The total number of disease manifestations, and ANA and/or SS-A autoantibodies were the best predictors of fatigue, but explained it only to 17-57%.

Conclusion

Patients with fatigue and perceived ill health but without fibromyalgia had sicca symptoms and low basal tear and salivary secretion rates,indicating that cortical events can lead to a SS-like sicca syndrome. Even in SS fatigue is only in part explained by clinical disease manifestations and laboratory tests assessing inflammation and autoimmunity. Fatigue in both SS and non-SS sicca syndrome more likely correlates to other features, such as neuroendocrine aspects of the disease.

Introduction

Chronic fatigue and the perception of ill health - frequent complaints in many diseases - are often a major problem for the patient, having a devastating effect on every aspect of life.

Fatigue and ill mental health may affect the functioning of the exocrine glands. Besides reflectory masticatory and gustatory stimuli, the superior and inferior salivary nuclei are also controlled by general well-being and cortical and subcortical inputs associated with thoughts of an oncoming delicious dinner or fear and anxiety. Our hypothesis was that patients who suffer from dry eyes and dry mouth and have low basal lacrimal and salivary flow, but no Sjögren's syndrome (SS; 1) nor fibromyalgia (2), are tired and in ill health. Tiredness and ill mental health could lead to low basal secretion rate via cortical and subcortical inputs to salivary nuclei and could explain the sicca symptoms.

Fatigue has been reported to occur in over 50% of SS patients (52.5-83%; 3-6) and may be the first symptom (6). Extreme weariness was the main reason why SS patients had to give up working (6). 27.6% of 1° SS patients ranked tiredness above the sicca symptoms as the worst and most troublesome symptom (5). In present study we tried to evaluate two important related clinical questions: 1) What is the health status in non-SS, non-fibromyalgia patients with dry eyes and dry mouth associated with diminished basal secretory flow (non-SS sicca syndrome); and 2) to what extent fatigue in SS patients is explained by immune-inflammatory activity and the extent of their disease.

Patients and methods

Patients

Patients from the Sjögren's Syndrome Association were asked to participate in the study using an advertisement in the patient journal. 129 patients responded (90 1° SS and 24 2° SS: 16 rheumatoid arthritis, 5 systemic lupus erythematodes and 3 spondyloarthropathies) (1) (Table I). 15 subjects had dry eyes and dry mouth and decreased basal lacrimal and salivary flow, but lacked autoantibodies and autoimmune features. We excluded other diseases and conditions, such as HIV, HCV, lymphoma, sarcoidosis, graft-vs-host

Table I. Demographic data and medication of non-SS sicca syndrome patients, primary SS patients, and secondary SS patients (number of patients/% if not indicated otherwise).

	Non-SS	1° SS	2° SS
Number of patients	15	90	24
Age (years)	56 (37-79)	54 (24-87)	56 (19-78)
Gender (F/M)	15/0	86/4	22/2
GCS	2 /13.3	19/21.1	8/33.3
DMARD	3/20.0	20/22.2	17/70.8
NSAID	6/40.0	33/36.7	13/54.2
Diuretics	1/6.7	6/6.7	1/4.2
HRT	3/20.0	33/36.7	7/29.2
Anticholinergic drugs	0/0	4/4.4	0/0
Antihistaminic drugs	2/13.3	5/5.6	0/0
Antidepressants	2/13.3	9/10.0	3/12.5
Tranquillizers	4/26.7	4/4.4	4/12.5
L-thyroxine	1/6.7	12/13.3	2/8.3

F: female, M: male (the mean age and range for women was 46 years [range 16-84 years]); GCS: systemic glucocorticosteroids; DMARD: disease modifying anti-rheumatic drugs; NSAID: nonsteroidal anti-inflammatory drugs; HRT: hormone replacement therapy.

disease, diabetes, infections and anticholinergic medications as a cause of sicca symptoms. Diagnosis in all patients was done by one of the authors (YTK). None of the subjects fulfilled the classification criteria of fibromyalgia (2). In contrast to the patients with 1° SS and non-Sjögren's sicca syndrome, it was not possible to exclude the influence of the primary disease in patients with 2° SS. As population controls, 126 women were randomly selected from the Finnish Official Population Register. The mean age was 45 years and the range was 16-84. The healthy women (controls) were younger than the patients ($p = 0.0002$). In order to exclude the possible influence of age differences between the groups, analysis of the health profile was done with age as a covariate.

Clinical disease manifestations were recorded using the first version Oxholm wheel (7). Functional status of the glands was analysed using the Schirmer-I and Rose-Bengal tests and unstimulated and stimulated salivary flow measurements.

SF-36

The Medical Outcomes Study Short-Form General Health Survey (MOS SF-36) (8, 9) is a 36-item questionnaire measuring eight health concepts: physical functioning, role limitations due to physical health problems, role limitations due to emotional health problems, energy (the opposite of vital energy is a measure of fatigue), mental health, social functioning, bodily pain and general health perception. For each variable item scores are coded, summed and transformed to a scale from 0 (worst possible health state) to 100 (best possible health state).

Statistical analysis

The chi-square test was used to examine the relationship between fatigue and the diagnosis, Kruskal-Wallis one-way analysis of variance to compare different study groups, Spearman's rank correlation coefficient to assess relationships between vitality and other variables, and multiple linear regression analysis to evaluate the best possible predictors of vitality.

Results

Fatigue was experienced by 74% of the SS patients and 80% of the non-SS sicca patients. The salient findings were:

1) 1° and 2° SS had similar SF-36 profiles,
2) perceived health in SS was clearly worse than in the population control sample ($p < 0.001$),
3) the perceived health status was worst in non-SS, non-fibromyalgia patients, who suffered from sicca symptoms and had low basal lacrimal and salivary secretion rates (Fig. 1) ($p < 0.001$ for all health concepts compared to population controls and to SS: role limitations due to physical health problems ($p < 0.001$ against 1° SS and $p < 0.01$ against 2° SS), role limitations due to emotional problems ($p < 0.01$ against 1° SS and $p < 0.05$ against 2° SS), vital energy ($p < 0.05$), mental health ($p < 0.05$ against 2° SS) and bodily pain ($p < 0.05$).

Vital energy scores were 40 ± 20 in 1° SS and 42 ± 21 in 2° SS. The vitality score in non-SS sicca syndrome patients was lower: 29 ± 16. They also had pathological Schirmer-I test, Rose-Bengal staining score and non-stimulated salivary flow rate. Stimulated flow rate was relatively good (12.1 ml/5 min, range 4.8-18.3).

According to Spearman's rank correlation coefficients the following variables showed significant correlations with fatigue: in 1° SS serum IgG ($p < 0.05$) and ANA ($p < 0.01$), and in 2° SS the number of disease manifestations (negative correlation; $p < 0.005$). In multiple linear regression analysis, ANA explained 9% of fatigue and the total number of symptoms explained an additional 10% of fatigue. In 1° SS the corresponding figures were 9% and 8%. In 2° SS, SS-A autoantibodies explained 35% of fatigue and total symptoms contributed an additional 22% (Table II). In a mathematical model 17-57% of fatigue was explained by variables recorded in the present study. Conversely, 43-83% of the fatigue could not be explained by those variables.

Discussion

In the present study we demonstrate that patients with a subjective feeling of dry eyes and dry mouth and with verified diminished basal lacrimal and salivary flow rates suffer from ill health and fatigue. Stimulated salivary flow was relatively well preserved, suggesting that fatigue and ill mental health affect the basal tone of the salivary nuclei. The autonomic nerves have a basal tone which is regulated by the level of

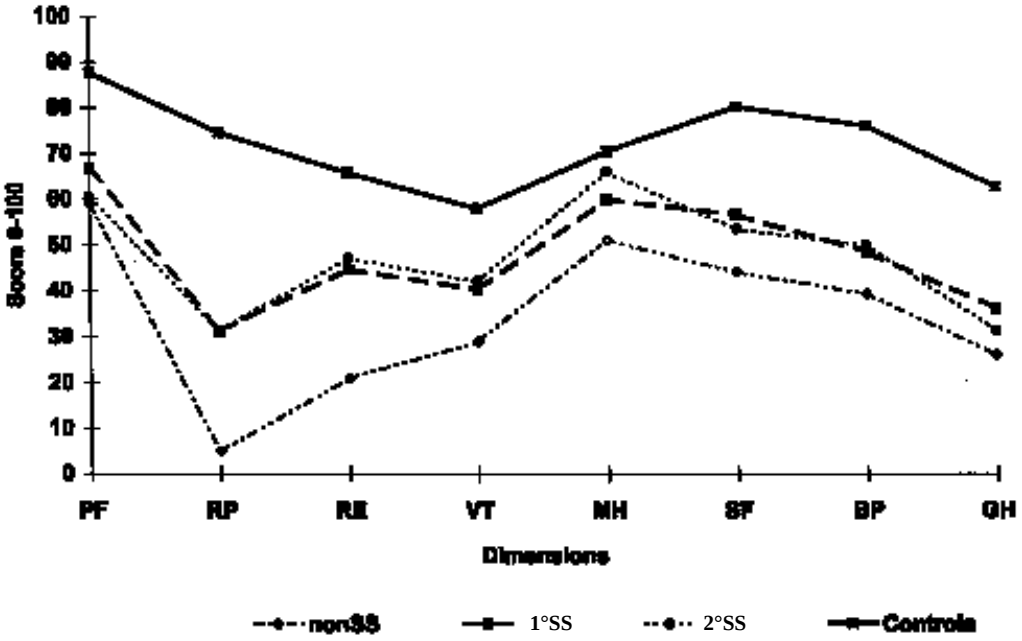

Fig. 1. Short-form-36 health profiles in population controls (126 women), primary Sjögren's syndrome patients (n = 90),secondary Sjögren's syndrome (n = 24) and non-Sjögren's syndrome patients,and non-fibromyalgia patients with dry eyes and dry mouth and with decreased basal lacrimal and salivary flow rates (n = 15). The health profile was very similar for the normal control population when men were also included (data not shown).
PF = physical functioning; RP = role limitations due to physical health problems; RE = role limitations due to emotional problems; VT = vitality; MH = mental health; SF = social functioning; BP = bodily pain; GH = general health perception.

activity of the superior and inferior salivary nuclei in the central nervous system. The activity level of these nuclei is regulated by masticatory and gustatory stimuli which induce the reflectory salivary flow, and are also controlled by cortical and subcortical stimuli, with for example thoughts of delicious food being able to lead to increased salivation whereas depression, fear and anxiety lead to decreased salivation.

These non-SS sicca patients had muscle and joint pain, although they did not fulfill the criteria for fibromyalgia (2). The original EU classification criteria (1) need to be supplemented with some autoimmune findings. Otherwise a depressed, anxious or tired and "burned-out" patient may be inadvertently classified as having SS. The prevalence of such patients is not known, but based on the present survey it can be concluded that they are not rare.

Table II. Results of linear regression analyses with fatigue as the dependent variable.

All SS patients			
$R = 0.45$, $R^2_{adj} = 0.19$, $F = 12.6$, $df = 2, 100$, $p < 0.0005$			
ANA	0.32	0.34	9%
Total symptoms	-0.36	-0.37	10%
Only primary SS patients			
$R = 0.42$, $R^2_{adj} = 0.15$, $F = 8.3$, $df = 2, 78$, $p < 0.005$			
ANA	0.35	0.35	9%
Total symptoms	-0.29	-0.30	8%
Only secondary SS patients			
$R = 0.75$, $R^2_{adj} = 0.52$, $F = 12.4$, $df = 2, 19$, $p < 0.001$			
SS-A autoantibodies	0.55	0.58	35%
Total symptoms	-0.89	-0.75	22%

ANA:anti-nuclear antibodies; total symptoms:total number of disease symptoms/ findings as assessed using the first version of the Oxholm wheel.

1° SS patients are tired and this is not only explained by depression (10). All subgroups of SS patients had lower values on the SF-36 (8, 9) compared with the normal population (11). Although patient recruitment methods may have led to serious bias, at least in this patient population parameters reflecting inflammatory or immune system activation did not seem to explain fatigue. On the contrary, higher values for ANA and SS-A autoantibodies turned out to correlate with higher vital energy.

One explanation of the fatigue in SS patients could be an imbalance in cytokine concentrations and dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis. Increased levels of serum IL-6 and an increased frequency of cells secreting IL-6 and IL-10 have been found in 1° SS patients. IL-6 and IL-2 are associated with increased fatigue. TNF- stimulates production of these interleukins and has also a large variety of other biological effects including somnogenic (12, 13). TNF- , IL-1 and IL-6 stimulate specific receptors in the central nervous system to release corticotropin, growth hormone and cytokines, thus providing a link between the immune system and the

neuroendocrine system (14, 15). The next steps in the studies on fatigue associated with SS could be the measurement of serum cytokine levels and the functioning of the HPA axis (14-16).

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