Fatigue in Sjögren's syndrome: relationship with fibromyalgia, clinical and biological features

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This work was supported by the Fondazione Umberto Di Mario.

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Received on September 14, 2010; accepted in revised form on December 1, 2010.

Clin Exp Rheumatol 2010; 28 (Suppl. 63): S82-S86.

Key words: **S**jögren's syndrome, fibromyalgia, fatigue, disease activity, cytokines

Competing interests: none declared.

ABSTRACT

More than two third of patients with primary Sjögren's syndrome (SS) report fatigue. Despite its clinical relevance, only a few studies have examined the relationship of fatigue with the presence of an overlapping Fibromyalgia (FM) and other clinical and biological variables. The aim of this study was to assess the relationship between fatigue and SS disease activity and damage, FM, widespread pain, and mood disorders; finally, the possible correlation between fatigue and a panel of cytokines likely to drive the immunopathological process of the disease has been examined.

Thirty-five female patients with primary SS were consecutively enrolled; for each patient the Sjögren's Syndrome Disease Damage Index (SSDDI) and the Sjögren's Syndrome Disease Activity Index (SSDAI) were calculated. Patients rated pain, fatigue and disease activity using a 100-mm VAS and completed Health Assessment Questionnaire (HAQ), the Zung depression (ZSDS) and anxiety scales (ZSAS). 30/35 patients (85.7%) felt unduly tired and the same percentage of patients suffered with pain in more than one area of the body. 7 patients satisfied ACR criteria for FM, representing 20% of the whole cohort and 23% of SS patients with fatigue. No differences were found in disease duration, SSDDI, SSDAI, ZSDS and ZSAS among SS patient with or without FM. In the whole group, fatigue VAS correlated with HAQ, ZSAS, ZSDS and pain VAS but not with age, disease duration, presence and severity of arthritis, SSDDI, SSDAI, or cytokines. In conclusion, an overlapping FM can contribute to, but does not entirely account for fatigue in Italian patients with primary SS.

Introduction

Sjögren's syndrome (SS) is an autoimmune disease primarily affecting the exocrine glands and usually presenting as persistent dryness of the mouth and eyes (1). The exact incidence of SS remains unclear, while the prevalence can be estimated at 0.5–1%; middle aged women are overwhelmingly affected compared to men (9:1) (2).

Although most patients present with sicca symptoms, SS is a systemic disorder associated with a wide spectrum of extraglandular manifestations such as arthralgia or frank arthritis, cytopenia, Raynaud's phenomenon, nervous system involvement, skin vasculitis (3). Among the most common symptoms not included in the current classification criteria (4), fatigue and generalised pain represent an important cause of impaired quality of life (5-7) but their underlying mechanisms are still obscure. An association between Fibromyalgia (FM) and SS has been reported with conflicting evidences (8-10), while others have described mild histopathological signs of myositis in patients affected by SS (11). A Swedish study hypothesized that symptoms of fatigue experienced by women with SS could be explained by functional disability, depression, age, and reduced aerobic capacity (12), while a subsequent study demonstrated that depression is not the primary cause of fatigue (7).

Finally, some authors have hypothesizgged that fatigue, poorly characterised pain, anxiety and depression frequently affecting SS patients may be explained by autonomic nervous system disturbances (13). However, all these studies have led to inconclusive results. The relationship between fatigue and other clinical and laboratory features in SS needs to be further evaluated, and, in particular, a clearer definition is needed concerning the link between 'biological' disease activity and fatigue. Some studies demonstrated a correlation between fatigue severity and se-

rum levels of immunoglobulins, ANA, lymphocyte counts and anti-Ro (SSA) antibodies (7, 14-16). However, such factors can be considered as surrogate 'disease activity' markers and it is still unclear if they faithfully reflect disease activity in SS. Indeed, no standardised tool for measuring disease activity were available until the recent publication of the SS Disease Activity Index (SSDAI) (17) and the EULAR SS Disease Activity Index (SSDAI) (18). Even fewer data are available regarding the relationship between fatigue and molecules - such as cytokines - possibly involved in the disease pathogenesis.

In the present study we first evaluated the relationship between fatigue and SS disease activity and damage using the recently devised activity and damage scoring system; secondly, we assessed the link among fatigue and presence of overlapping FM, widespread pain, anxiety, and depression; finally, a possible correlation between fatigue and a panel of cytokines likely to drive the immunopathological process has been examined.

Materials and methods

Patients

Patients with primary SS (diagnosis according to the Euro-American criteria) (4) attending the Sjögren's syndrome clinic of our Rheumatology Department were consecutively enrolled. All participants were evaluated with a detailed medical history regarding organ manifestations and current medication. Patients reporting changes in their systemic treatment during the previous 3 months, or taking more than 10 mg prednisolone per day were excluded, as well as those with an overt thyroid dysfunction. After obtaining informed consent, Sjögren's Syndrome Disease Damage Index (SSDDI) and the SSDAI were calculated for each patient (17). Patients were asked if they had been feeling fatigued or unduly tired on most days for the last 3 months; they were also asked if they had been suffering with generalised body pain in the same period (9). As in a previous study (7), patients rated fatigue, pain, and disease activity using a 100-mm Visual Analogue Scale (VAS) and completed the HAQ and the validated Italian version of the Fibromyalgia Impact Questionnaire (FIQ) (19, 20). Furthermore, the Zung depression and anxiety scales (ZSDS, ZSAS) were used to quantify aspects of mood disorders (21, 22). Pressure pain threshold was determined at the 18 ACR tender points (TP) using an algometer. A patient was deemed to have FM when fulfilling ACR classification criteria for the disease (23). All patients signed an informed written consent according to Local Ethical Committee Guidelines.

Serological analysis

Venous blood was drawn at the time of the clinic visit. Complete blood count, erythrocyte sedimentation rate (ESR) and C Reactive Protein (CRP) were performed using standard methodologies. All sera were blindly analysed for IgG ANA by indirect immunofluorescence on Hep2 cells (serum dilution 1:80) (Bio-Rad laboratories). Rheumatoid factor (RF) (Behring, germany) and anti-ENA (anti-Ro/SSA, anti-La/SSB) (Diamedix. Miami, Florida) were detected by ELISA following the manufacturer's instructions. Serum concentrations of IL-1β, IL-6, IL-8, TNF-α, IFN-γ were quantified using a multiplex bead-based sandwich immunoassay kit (Bio-Rad Laboratories Inc., Hercules, CA, USA). Each sample was assayed in duplicate according to manufacturer's instructions. Data were analysed with Bio-Plex manager software, version 4.1.1 (Bio-Rad laboratories). Values with a coefficient of variation >12% were excluded from the final data analysis. The concentrations (pg/ml) of different analytes in the serum samples were determined with the aid of standard curves generated in the multiplex assays. Serum IL-18 was quantified using ELISA (R&D Systems, Inc. Minneapolis).

Statistical analysis

The χ^2 test was used for testing the significance of correlations between clinical and serological features. Differences between groups were analysed with the Mann-Whitney U-test. The Spearman test was used for correlation analysis. A p-value <0.05 was considered statistically significant. In addition, principal component analysis for categorical data (Categorical Principal Component Analysis, CATPCA) was used to assess the behaviour of clinical and serological parameters. CATPCA uses optimal scaling to generalise the principal components analysis procedure so that it can accommodate variables of mixed measurement levels. This analysis is somewhat similar to multiple correspondence analysis and it allows to display results in a low-dimensional map that facilitates establishing relationships among multiple variables. SPSS (release 13.0) was used.

Results

Thirty-five consecutive Italian primary SS patients (*i.e.* with no association with other connective tissue diseases) were enrolled, presenting with a mean age of 53 years (range 27–70 years) at examination. Average disease duration was 11 years (range 3–31 years). Thirty out of 35 (85.7%) patients felt unduly tired with a mean fatigue VAS of 68.3 (range 5–100). The remaining 14.3% (5/35) patients denied having fatigue. 85.7% (30/35) of patients reported pain in more than one body site area on most days with a mean pain VAS 55,7 (range 5–100), while 14.3% (5/35) denied generalised pain. Patients complaining fatigue or diffuse pain did not completely overlap.

Seven patients were diagnosed with FM having presented chronic widespread pain and tenderness of at least 11 out of the 18 TP for more than three months. This group represented 20% of the whole cohort and 23% of the SS fatigued patients.

As shown in Table I, no differences were found in disease duration, SSDDI, SSDAI, ZSDS and ZSAS results among SS patients with or without FM. Obviously, the number of TP was statistically significantly different between the two groups.

In the whole group, VAS fatigue was related to HAQ, ZSAS, ZSDS, and VAS pain, but not to age, disease duration, presence and severity of arthritis, SSDDI, SSDAI (Fig. 1). Moreover, VAS fatigue did not correlate with ESR, CRP, presence of anti-Ro/SSA and/or

Table I. Features of Sjögren's syndrome patients with and without fibromyalgia.

Features	28 pSS patients Median (range)	7 pSS-FM patients Median (range)	*p*-value
Age (yrs)	57 (27–70)	59 (34–68)	NS
Disease duration (yrs)	3 (0–18)	10 (2–15)	NS
SSDDI	1 (0–5)	1 (0–3)	NS
SSDAI	1 (0–4)	1 (0–4)	NS
HAQ	0.25 (0–1.6)	0.5 (0–2.1)	NS
Fatigue VAS	55 (0–100)	90 (10–100)	NS
Pain VAS	40 (0–100)	65 (10–100)	NS
ZSAS	49 (26–71)	53 (45–78)	NS
ZSDS	54 (25–75)	53 (34–86)	NS
TP number	4 (0–10)	12 (11–16)	0.0001

SSDDI: Sjögren's Syndrome Disease Damage Index; SSDAI: Sjögren's Syndrome Disease Activity Index; HAQ: Health Assessment Questionnaire; VAS: 100-mm Visual Analogue Scale; ZSAS: Zung Self-Rating Anxiety Scale; ZSDS: Zung Self-Rating Depression scale; TP: tender points.

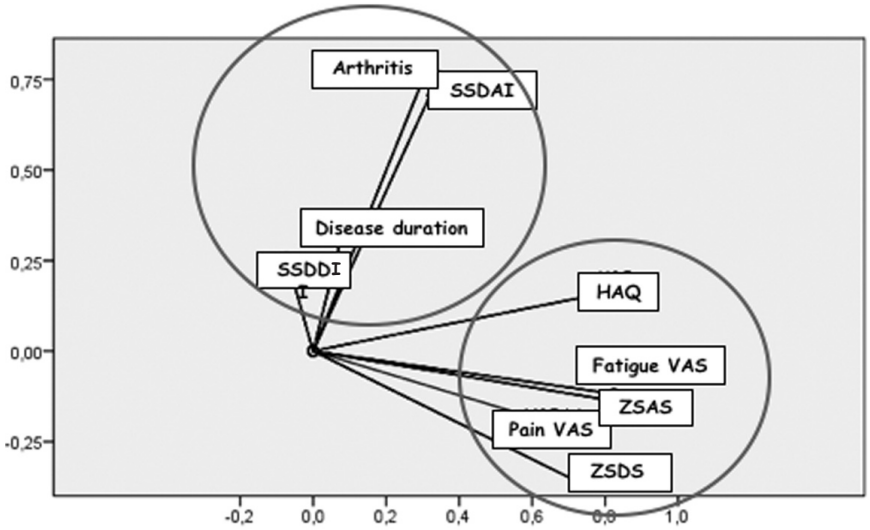

Fig 1. CATPCA analysis, used to assess the behaviour of clinical and serological parameters, demonstrated that VAS fatigue was related with HAQ, ZSAS, ZSDS, and VAS pain, but not with age, disease duration, presence and severity of arthritis, SSDDI, SSDAI.

anti-La/SSB, RF, and cytokine serum levels (*p*=ns). No difference was found in cytokine serum levels between pSS patients with and without fatigue and with and without FM. Finally, no correlation was observed between pSS patients' clinical features and cytokine serum levels (data not shown).

Discussion

A definition of the "fatigue" is not an easy one, as it involves both physical and mental features. It is a common, invalidating symptom associated with a wide range of chronic diseases. In population-based studies, 11–20% of healthy adults reported persistent fatigue (24, 25). Among patients with autoimmune diseases, prevalence of fatigue is much higher, in the range of 60–70% (26-28), and in primary SS fatigue is reported by 68–74% of the patients as worsening their overall quality of life (5, 9, 14, 29). A slightly higher prevalence of fatigue has been found in our cohort of Italian patients with primary SS: this difference might be explained by cultural differences, or by the methodology used for fatigue assessment. In fact, as it represents a subjective experience, fatigue is rather difficult to be measured, despite the availability of a large number of assessment tools (30-32).

One of the limits of this study was the use of a single method for measuring fatigue, *i.e.* the 100-mm Visual Analogue Scale (VAS), with the anchor points being 'No fatigue' and 'Worst possible fatigue'. The VAS is one of the simplest and most popular methods for measuring fatigue severity, even if it does not describe in detail the dimension of experienced fatigue (*e.g.* physical, mental, motivational and affective). However, VAS has been largely used in other inflammatory autoimmune disorders and it seems to perform better for the assessment of physical rather than mental fatigue. Actually, results from studies using multi-dimensional assessment tools showed that physical/somatic fatigue is more severe and frequent than mental fatigue in patients with primary SS (7, 14, 33, 34). Therefore, using only the VAS for measuring fatigue in our population should not affect the conclusions of the study.

As far as we know, this is the first study linking fatigue with disease activity using a standardised scoring system instead of surrogate disease activity markers. We did not find any correlation between fatigue and disease activity scored with SSDAI (17), nor did we detect any link between fatigue and damage scored with SSDDI (17).

No correlation was found between fatigue and ESR, anti-Ro/La or RF, and this result is in line with previous studies which did not detect any relationship between fatigue and laboratory values, (5, 35) with the exception of an isolated report of a positive link between fatigue severity and lymphopenia (7).

We also investigated serum levels of some cytokines. These molecules play a central role in the regulation of the immune response, and a dysregulation of the cytokine network may contribute to both systemic and exocrine manifestations of SS. The link between cytokines and fatigue is supported by experimental models in which administration of IL-1β or TNF-α leads to decreased activity and increased somnolence (36). Such correlation is also supported by *in vivo* observations: in man, cytokine treatment with TNF-α (37), IL-2 (38), or IL-6 (39) is associated with fatigue, depressed mood, and cognitive disturbances. Moreover, it is well known that in patients with rheumatoid arthritis fatigue is reduced by TNF-α blocking therapy (40). The cytokine imbalance in

SS is characterised by over-expression of pro-inflammatory cytokines such as IFN-γ, IL-2, IL-10, IL-12 and IL-18. Two other cytokines, IL-6 and BAFF, which are important in T- and B-cell activation and autoantibody production, are also up-regulated (41). Only a few works have addressed the role of inflammatory cytokines in the pathogenesis of fatigue in primary SS. Serum IL-1β, IL-2, IL-6, IL-10, and TNF-α levels do not seem to have an impact on any aspect of fatigue, (42), while IL-6 system has been found to counteract SS-associated fatigue (43). In this study, serum cytokine concentration did not correlate with fatigue severity as scored by VAS. We can hypothesize that circulating levels of cytokines may not reflect the local condition of the central nervous system: actually, increased levels of IL-1 receptor antagonist in the cerebrospinal fluid have been found associated with increasing fatigue in pSS patients (44).

As the cause of fatigue in primary SS is likely to be multidimensional, a concomitant FM could partly account for it. Previous studies have demonstrated a prevalence of FM in primary SS higher than that found in this study (44%–55% *vs*. 20%) (45). This discrepancy may be explained by differences in the sample size, but also by cultural and geographical aspects; actually, our results are in line with those previously reported in an Italian study (8) where ACR criteria for FM were strictly used, as well as with a study performed in the UK (9).

FM is defined as a common chronic widespread pain disorder without structural pathology but very disabling for the patients (46, 47). It is also characterised by other features overlapping with SS such as fatigue, sleep disturbances, morning stiffness, paresthesias, headache, anxiety, irritable bowel, Raynaud's phenomenon and sicca symptoms (47). The pathophysiology of FM as well as that of other chronic pain syndromes is still unclear; current theories include a combination of interactions between neurotransmitters (48), external stressors, behavioural constructs, hormones, autonomic nervous system (ANS) (49, 50), oxidative system, antibodies and cytokines (51). A possible role for cytokines has been considered because of the appearance of FM-like symptoms in patients with malignancies or chronic hepatitis treated with cytokines (52, 53) but their true importance in FM pathogenesis remains unclear and recent studies show controversial results. According to our study, serum cytokine concentration does not differ in primary SS patients between those with or without FM.

In agreement with previous studies (5, 54), a significant link was found between the degree of fatigue and the level of depression and anxiety in this group of Italian patients with primary SS. On the contrary, Segal *et al*. demonstrated that, although higher level of fatigue correlated with depression, the majority of the fatigued subjects were not depressed (7). The coexistence of the two symptoms, fatigue and depression, does not necessarily imply causality: we can either hypothesize that both symptoms share some common pathogenetic factors, *i.e*. neuroendocrine dysfunction or, alternatively, that chronic fatigue might lead to the development of depression (31). In conclusion, no relationship was found between fatigue and SS disease activity and damage using the recently devised scoring tools SSDAI/SSDDI; an overlapping FM can contribute to, but do not entirely account for fatigue in Italian patients with primary SS; widespread pain, anxiety, and depression were related to the severity of fatigue as assessed with VAS; finally, serum cytokines level does not seem to modulate fatigue in pSS or explain an association with FM.

This study highlights that presence of TP is the main feature of SS patients with FM overalapping. In the evaluation of the possible cause of fatigue in SS, other factors should be taken into account in future studies such as cerebral white matter hyperintensities – which have been found to be increased in SLE fatigued patients (55) – sleep disorders, subclinical autonomic disturbances or abnormalities in the neuroendocrine system. However, SS patients with fatigue and widespread pain should be evaluated also for FM overlapping in order to avoid misdiagnosis.

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