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Abstract

Objective—To assess fatigue in relation to depression, blood pressure, and plasma catecholamines in patients with primary Sjögren's syndrome (SS), in comparison with healthy controls and patients with rheumatoid arthritis.

Methods—For the assessment of fatigue the Multidimensional Fatigue Inventory (MFI) was used, a 20 item questionnaire, covering the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Furthermore, the Zung depression scale was used to quantify aspects of depression. Forty nine female primary SS patients, 44 female patients with rheumatoid arthritis (RA), and 32 healthy women filled in both questionnaires. In addition, supine values of blood pressure and plasma catecholamines were measured in the patients with primary SS.

Results—Primary SS patients were more fatigued compared with the healthy controls on all the five dimensions of the MFI. When the analyses were repeated using depression as a covariate, group differences disappeared for the dimensions of reduced motivation and mental fatigue. In the primary SS patients, significant positive correlations between depression and the dimensions of reduced motivation and mental fatigue were found. Comparing patients with primary SS with those with RA, using depression as covariate, no statistically significant differences were found between these groups. No relation between fatigue and blood pressure was found, but a negative correlation was observed between the general fatigue subscale of the MFI and plasma noradrenaline.

Conclusion—Patients with primary SS report more fatigue than healthy controls on all the dimensions of the MFI and when controlling for depression significant differences remain on the dimensions of general fatigue, physical fatigue, and reduced activity. The negative correlations between levels of noradrenaline and general fatigue in patients with primary SS may imply the involvement of the autonomic nervous system in chronic fatigue. (*Ann Rheum Dis* 1998;57:291-295)

Fatigue is the enduring, subjective sensation of generalised tiredness or exhaustion.¹ Whereas occasional fatigue is a part of the experiences of every day life, constant or frequent fatigue is not.

Chronic fatigue in rheumatoid arthritis (RA) patients is a serious problem, because it contributes to work disability, personal injury, inability to participate in a rehabilitation programme, and strained relationships.²

Most patients with rheumatic diseases complain of chronic fatigue³ and most studies concerning fatigue in rheumatic diseases report that disease activity, sleep disturbances, depression, and increased physical effort most strongly contribute to complaints of fatigue.⁴

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease characterised by lymphocytic infiltration of endocrine glands. Keratoconjunctivitis sicca and xerostomia generally are considered to be dominant features, but patients may suffer from many extraglandular features such as arthritis, exanthema, respiratory tract involvement, and neuropsychiatric symptoms.⁵ In contrast with other autoimmune diseases such as RA, in primary SS valid parameters for disease activity are lacking. In primary SS, fatigue is an important, and sometimes the most disabling, symptom of the disease,⁶ but studies on fatigue and its characteristics in these patients are rare.

It has recently been suggested that chronic fatigue may be related to low blood pressure and to abnormalities of the autonomic nervous system.⁷⁻¹⁰ As the presence of autonomic dysfunction has been reported in rheumatic diseases including RA,¹¹ systemic lupus erythematosus (SLE),¹² systemic sclerosis,¹³ and primary SS,¹⁴ it may be hypothesised that there is a link between autonomic dysfunction and fatigue in these diseases.

The aim of this study was to assess the level of fatigue in primary SS patients and its association with depression, disease activity, and autonomic function. Therefore characteristics of fatigue in primary SS were compared with those in patients with RA with different levels of disease activity and to the fatigue levels in normal subjects.

Methods

PATIENTS

Three groups of women were studied:

Group 1: 49 consecutive women with primary SS according to the European Criteria,¹⁵ aged 20-85 years (median 54), with a disease duration of 1-30 years (median 5), from the outpatients clinic of the Department of Rheumatology, Dr Daniel den Hoed Clinic, Rotterdam. All patients had more than one focus of ≥ 50 mononuclear cells per 4 mm² salivary gland tissue of the lower lip¹⁶ (30 positive out of 34 tested) and/or an abnormal parotid gland sialography¹⁷ (37 positive out of 45 tested), as well as at least one of the following serological abnormalities: antinuclear antibodies (ANA,

Department of Rheumatology, Zuiderziekenhuis, Rotterdam, the Netherlands
P J Barendregt
H M Markusse

Department of Medical Psychology, Academic Medical Centre, Amsterdam, the Netherlands
M R M Visser
E M A Smets

Departments of Psychiatry
J H M Tulen

and Internal Medicine I
A H van den Meiracker
F Boomsma

University Hospital Rotterdam-Dijkzigt, Rotterdam, the Netherlands

Correspondence to:
P J Barendregt,
Department of Rheumatology, Zuiderziekenhuis, Groene Hilledijk 315, 3075 EA Rotterdam, the Netherlands.

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Instructions:

By means of the following statements we would like to get an idea of how you have been feeling lately. There is, for example, the statement:

"I feel relaxed"

If you think that this is entirely true, that indeed you have been feeling relaxed lately, please place an X in the extreme left box; like this:

yes, that is true no, that is not true

The more you disagree with the statement, the more you can place an X in the direction of "no, that is not true". Please, do not miss out a statement and place one X next to each statement.

1. I feel fit yes, that is true no, that is not true
2. Physically I feel only able to do a little yes, that is true no, that is not true
3. I feel very active yes, that is true no, that is not true
4. I feel like doing all sorts of nice things yes, that is true no, that is not true
5. I feel tired yes, that is true no, that is not true

Figure 1 Example of the Multidimensional Fatigue Inventory.

35 out of 49 positive), rheumatoid factor (RF, 24 out of 46 positive), or antibodies to SS-A (32 out of 49 positive) or SS-B (17 out of 49 positive) antigens. The median and range of erythrocyte sedimentation rate, β -2 microglobulin, and haemoglobin in this patient group were 29 (11–110) mm 1st h, 1.8 (1.1–4.8) mg/l, and 7.6 (5.5–9.3) mmol/l respectively.

Group 2: 44 consecutive women with seropositive RA according to the ARA criteria,¹⁸ aged 24–92 years (median 65), with a disease duration of 2–54 years (median 14), derived from the same outpatient clinic.

Group 3: 32 healthy women, aged 26–82 years (median 57), who were relatives of patients or hospital employees, served as controls. None of the women asked to participate in the study refused.

Women were excluded from study participation when they suffered from neurological disease, amyloidosis, renal failure, diabetes mellitus or other diseases known to interfere with the autonomic nervous system or receiving drug treatment interfering with the autonomic nervous system including diuretics, antiarrhythmics, neuroleptics, anti-epileptic, and anti-depressive drugs.

The study was approved by the Medical Ethical Committees of the Dr Daniel den Hoed Clinic and the University Hospital Rotterdam-Dijkzigt.

QUESTIONNAIRES

At intake, all women completed the Multidimensional Fatigue Inventory (MFI) and the Zung depression scale. The MFI is a 20 item self report scale, designed to objectivate fatigue and covering the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each scale consists of two items indicating fatigue and two items contraindicating fatigue, to limit possible influence of answering tendencies. A higher score indicates a higher level of fatigue (range 4–20). The answers given should reflect feelings of the subjects over the past few days. The scale was previously tested and validated in populations of chronic fatigued patients, cancer patients, soldiers, and psychology students.¹⁹ In figure 1 examples of items of the different scales are presented.

The Zung-Self Rating Depression Scale was used as a quantitative measure of depressive symptomatology. The scale is also self administered and contains 20 items covering affective, psychological, and somatic features of depression.²⁰ Items concerning fatigue were excluded from statistical analysis.

CLINICAL INVESTIGATION

Blood pressure measurements

In the primary SS patients blood pressure measurements were done by means of continuous registration of arterial blood pressure

(brachial or radial artery) during 15 minutes of supine rest.

Plasma catecholamines

Blood samples (10 ml per sample) were obtained after 10 minutes in supine position for the determination of plasma catecholamine concentrations (noradrenaline, adrenaline). Blood was collected in chilled heparinised polystyrene tubes containing glutathione (1.2 mg/ml). The tubes were centrifuged within 30 minutes (4°C, 10 minutes, 3000 × g) and the plasma was stored at -70°C. Concentrations of noradrenaline and adrenaline were measured by high performance liquid chromatography with fluorometric detection as described previously.²¹

Disease activity

In patients with primary SS, erythrocyte sedimentation rate (ESR), haemoglobin (Hb), and β2-microglobulin (β2-m) in serum were used as parameters of disease activity. The level of disease activity of the patients with RA was determined by means of the Disease Activity Score (DAS) (range from 0–8), which incorporates the Ritchie articular index, the number of swollen joints, and the ESR.²²

STATISTICAL ANALYSIS

One way analyses of variance were performed with group as a between subject factor (primary SS *v* controls; RA *v* controls; primary SS *v* RA) on the different scales of fatigue. The same analyses were performed again using depression as covariate. Pearson's correlation coefficients were computed between the scores of the subscales of the MFI and the Zung scale and between the scores of the subscales of the MFI and Hb, β2-m, ESR, age, disease duration, blood pressure level, and concentrations of plasma noradrenaline and adrenaline respectively. A p value of <0.05 was considered to indicate significance.

Results

Table 1 shows the scores of the MFI and the Zung depression scale. Table 2 gives the results of blood pressure, heart rate, and plasma catecholamine measurements in the primary SS patients.

For each scale of the MFI, the patients with primary SS had significantly higher scores compared with the healthy controls (p < 0.001).

Table 1 Scores of the Multidimensional Fatigue Inventory and the Zung Depression Scale in patients with primary Sjögren's syndrome, patients with rheumatoid arthritis, and healthy controls

	Primary Sjögren syndrome (n=49)	Rheumatoid arthritis (n=44)	Controls (n=32)
General fatigue	15.57 (4.3)*	12.93 (4.5)‡	8.16 (3.8)
Physical fatigue	14.06 (4.4)*	12.45 (5.0)§	6.47 (3.2)
Reduced activity	11.32 (4.6)†	11.48 (4.7)‡	6.72 (3.0)
Reduced motivation	9.96 (4.0)	9.27 (4.1)	6.66 (2.4)
Mental fatigue	10.31 (5.4)	8.34 (4.0)	6.53 (3.0)
Zung score	61 (18)*	55 (19)§	34 (12)

All values represent mean (SD) (depression used as a covariate). Primary SS *v* controls: *p ≤ 0.001 †p ≤ 0.05. Primary SS *v* rheumatoid arthritis: ‡no statistically significant differences. Rheumatoid arthritis *v* controls: §p ≤ 0.001, ¶p ≤ 0.001

Table 2 Results of blood pressure, heart rate, and plasma catecholamine measurements in 49 patients with primary Sjögren syndrome

	Supine position
Systolic blood pressure	130 (104–175)
Diastolic blood pressure	65 (49–85)
Heart rate	70 (52–101)
Adrenaline	32 (5–115)
Noradrenaline	151 (28–470)

All values represent median and (range). Blood pressure in mm Hg. Adrenaline and noradrenaline in pg/ml.

To correct for the influence of depressive symptoms, analyses were performed controlling for depression by including it as covariate. By so doing, the statistical significance of the group difference disappeared for the dimensions of reduced motivation and mental fatigue, but not for general fatigue, physical fatigue, and reduced activity (table 1). If clinical significant fatigue is defined as the mean (2 SD) of healthy controls, 57% of the primary SS patients suffered from fatigue.

The primary SS patients showed also significantly higher scores on the Zung depression scale compared with the healthy controls (table 1).

In the patients with primary SS, significant positive correlations were found between the scores of the MFI and the Zung depression scale, varying from 0.41 (p < 0.01) for the dimension of general fatigue to 0.49 (p < 0.001) and 0.61 (p < 0.001) for the dimensions of reduced motivation and mental fatigue respectively.

No significant correlations were found in the patients with primary SS between the fatigue scores and the Hb, β2-m, and ESR (used as measures of the disease activity), age, and disease duration respectively, nor with systolic blood pressure measurements or heart rate in supine position. A significant negative correlation was found between the concentrations of plasma noradrenaline in the supine position (r = -0.38, p < 0.05) and the subscale general fatigue, but no significant correlations were found between the plasma concentrations of adrenaline and general fatigue.

When comparing patients with primary SS with patients with RA, the first group had higher scores on the dimensions of general fatigue (p = 0.005) and mental fatigue (p = 0.05) compared with the second group. When the analyses were performed by controlling for depression, no significant differences remained between these patient groups (table 1). No significant differences in depression were found between the two patient groups.

For each scale of the MFI, patients with RA showed significantly higher scores compared with the healthy controls (general fatigue, physical fatigue, and reduced activity: p < 0.001, reduced motivation: p < 0.005, mental fatigue: p < 0.05).

When the analyses were performed by controlling for depression by including it as covariate, the statistical significance disappeared for the dimensions of reduced motivation and mental fatigue, but not for general fatigue, physical fatigue, and reduced activity

(table 1). The RA patients showed also significantly higher scores on the Zung depression scale compared with the healthy controls (table 1). For all the scales of the MFI, a correlation was found with the Zung depression scale, varying from 0.58 (general fatigue, $p < 0.001$) to 0.74 (reduced motivation, $p < 0.001$).

In the patients with RA the DAS scores were varying between 1 and 6.2 (mean 3.1), indicating that RA patients with both quiet and active RA were included. Significant positive correlations were found between the DAS score and general fatigue ($r = 0.43$, $p < 0.05$), physical fatigue ($r = 0.47$, $p < 0.01$), and reduced activity ($r = 0.42$, $p < 0.05$), respectively. No significant correlations were observed between the DAS score and reduced motivation and mental fatigue, nor between the DAS score and the results of the Zung scale.

Discussion

Considering our definition of fatigue, more than 50% of the primary SS patients in this study suffered from fatigue, indicating the importance of this symptom. In this study we found no differences in fatigue scores between patients with primary SS and patients with RA, both groups report significantly more fatigue than healthy controls.

Fatigue is, among others, a symptom of depression. In this study a subdivision could be made between the more physical aspects (physical fatigue and reduced activity) and the more mental aspects (reduced motivation and mental fatigue) of fatigue. Both patient groups (primary SS and RA) scored high on the depression questionnaire in comparison with the healthy controls and in those patient groups a correlation was found between depression and all subscales of fatigue. In the patients with primary SS, this correlation between depression and fatigue was statistically most significant for the two mental scales of the fatigue index.

By using depression as a covariate, the analyses showed no differences in mental fatigue and reduced motivation between the three groups investigated, but after this correction for depression, significantly higher scores were found in the two patient groups compared with the healthy controls for the dimensions of general fatigue, physical fatigue, and reduced activity.

Moreover, in the RA patients a positive correlation was found between the level of disease activity and the physical aspects of fatigue mentioned above. This concurs with previous studies on fatigue in both RA and SLE in which the disease activity of these patients also correlated with the severity of the fatigue.^{2 23 24} In this study we found no clear relations between the MFI scores and the laboratory parameters used in the primary SS group. These results are in line with a previous study that found no association between ESR, Hb, and the levels of antinuclear antibodies and rheumatoid factors and tiredness in primary SS.²⁵ It may be hypothesised that in primary SS aspects of fatigue are a better indicator of disease activity than the laboratory parameters.

We did not analyse the sleeping patterns of our patients; possibly sleep disturbances might have contributed to the fatigue observed in our patients.

A disturbance in the neuroendocrine system as a cause of fatigue in primary SS has been suggested.²⁶ Although we observed no association between the level of fatigue and blood pressure measurements, a significant negative correlation was found with plasma concentrations of noradrenaline. Though there might be influence of multiple testing, we think we found a relation between general fatigue and low noradrenaline values and this may point to a link with subclinical disturbances of the autonomic nervous system and fatigue.

In conclusion, fatigue is a serious problem in patients with primary SS. Some aspects of fatigue, such as mental fatigue and reduced motivation can most probably be attributed to depressive symptoms, but physical fatigue, general fatigue, and reduced activity may be related to disease activity in patients with primary SS. Further studies to elucidate whether specific aspects of fatigue may indeed be used as one of the parameters of disease activity in primary SS are warranted. The negative correlation between plasma noradrenaline values and the fatigue scores suggests a possible autonomic dysfunction in fatigued primary SS patients. Further studies in larger patient populations are necessary to elucidate this possible association.

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