Fatigue in Patients with Systemic Lupus Erythematosus: Lack of Associations to Serum Cytokines, Antiphospholipid Antibodies, or Other Disease Characteristics

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ABSTRACT. ***Objective***. To determine if fatigue in patients with systemic lupus erythematosus (SLE) is associated with levels of serum cytokines, antiphospholipid antibodies (aPL), or other disease features.

Methods. In a cross sectional study 57 Caucasian patients with SLE were subjected to clinical neurological examination and cerebral magnetic resonance imaging (MRI). Fatigue was evaluated by Fatigue Severity Scale (FSS) and disease activity by SLE Disease Activity Index (SLEDAI). Serum levels of tumor necrosis factor-α (TNF-α), interleukin 2 (IL-2), IL-6, IL-10, transforming growth factor-ß (TGF-ß), interferon-α (IFN-α), anticardiolipin antibody (aCL) IgG and IgM, as well as anti-$ß_2$-glycoprotein I antibody (anti-$ß_2$-GPI) IgG and IgM were analyzed by ELISA.

Results. Four of 5 patients with SLE had fatigue (FSS score ≥ 3). There were no associations between fatigue and any sociodemographic variables, medication for SLE, disease activity, cerebral infarcts, serum cytokines, aCL or $ß_2$-GPI antibodies, or any routine hematological, biochemical, or immunological tests.

Conclusion. Fatigue is a common phenomenon in patients with SLE. There is no association to disease activity or other markers of disease or inflammation. Fatigue is a complex phenomenon, and cytokine involvement in brain tissue not reflected by cytokine serum concentrations in this study cannot be excluded. Alternatively, psychosocial factors may well be the dominant predictor of fatigue in patients with SLE. (J Rheumatol 2002;29:482–6)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS FATIGUE
NEUROPSYCHIATRIC LUPUS CYTOKINES ANTIPHOSPHOLIPID ANTIBODIES

Systemic lupus erythematosus (SLE) is a chronic inflammatory multiorgan disease of unknown etiology, in which disturbances of the immune system are thought to play a major role. Global or focal involvement of the brain occurs frequently and in various forms, and is preferably referred to as neuropsychiatric SLE (NPSLE). It is thought that these manifestations are mediated through several disease mechanisms[1-5].

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Fatigue is a disabling phenomenon in many patients with SLE, as well as in other chronic inflammatory rheumatic diseases[6-10]. It may be defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion[11]. It also affects a considerable proportion of patients with multiple sclerosis (MS) or malignant disorders[12-14]. Fatigue is the dominant phenomenon of the chronic fatigue syndrome (CFS). This condition is defined as debilitating fatigue not secondary to any known clinical condition, lasting for > 6 months, with an activity level reduced by > 50% in a previously healthy person and accompanied by flu-like symptoms and neuropsychological manifestations[15].

Even though fatigue is associated with poor sleep and affective or other psychosocial factors[7,9,16,17], it is notable that the phenomenon is a prevalent complaint in diseases of chronic inflammatory nature. Only a few studies have noted an association with disease factors in SLE[10,13], while relation to biochemical, immunological, or other disease markers has been reported in multiple sclerosis[12] and rheumatoid arthritis[6,18]. Several studies on CFS, despite conflicting findings, have indicated an activated immunological state most consistently affecting the cellular immune system[19]. Since disturbances of cytokine production with some shift towards type 2 cytokines like interleukin 6 (IL-6)

and IL-10, but also increased production of IL-2, tumor necrosis factor (TNF-α), and interferon-α (IFN-α) are well known in SLE[20-22], it is interesting that some studies on patients with CFS show cytokine abnormalities with increased production of transforming growth factor-ß (TGF-ß), interferon-γ (IFN-γ), IL-1α, IL-1ß, IL-6, TNF-α, IL-2, and neopterin[19,23,24]. Such studies, as well as studies using infusions of cytokines like TNF-α[25], IL-2[26], IL-6[27], and IFN-α[28] resulting in profound fatigue and, on the other hand, immediate disappearance of fatigue following administration of anti-IL-6 receptor antibody[29], indicate that cytokines directly or indirectly play a role in fatigue originating from the central nervous system (CNS). We investigated the role of selected cytokines and other variables of inflammation in fatigue in an unselected group of patients with SLE.

MATERIALS AND METHODS

The University Hospital of Tromsø offers local hospital service to roughly 150,000 inhabitants of Troms County, and central and regional hospital service to Troms, Finnmark, and part of Nordland counties with a total of 450,000 inhabitants. All the medical records of in- and outpatients with a diagnosis of SLE seen at this hospital from 1979 to 1995 were reviewed. Ninety-four patients fulfilled the 1982 revised criteria of the American College of Rheumatology (ACR) for SLE[30]. Seventeen patients were dead, 3 had moved to another part of the country, and 5 were excluded from the study due to foreign language, myasthenia gravis, Down's syndrome, or terminal cancer. Of the remaining 69 patients, 57 (83%) gave an informed consent to be included in the study approved by the regional research ethics committee. Of the 57 patients, all except one were outpatients, and the vast majority of these were recruited on a local or central hospital basis. All were Caucasians. Fifty (88%) were women and 7 (12%) were men. Ages ranged from 23.0 to 73.0 years with a mean of 47.2 ± 12.9 years. Mean disease duration was 14.7 ± 8.9 with a range of 2–36 years.

The most frequent associated diseases or complications to SLE were arterial hypertension in 12 patients (21%), glomerulonephritis in 10 (18%), coronary heart disease in 6 (11%), and valvular heart disease, osteonecrosis or lung fibrosis in 2 patients (4%). One patient had diabetes mellitus type 2. Five patients (9%) were well regulated on thyroxine-Na due to earlier hypothyroidism or operation for goiter, and 5 patients (9%) used beta blockers.

At the time of examination, 12 of the 57 patients (21%) were taking no medication for SLE. Ten patients (18%) used antimalarials as single drug, 14 patients (25%) prednisolone only, while 21 patients (37%) used combinations of prednisolone, antimalarials and/or azathioprine or other cytotoxics.

Patients underwent a standardized general and neurological examination. Disease activity was measured according to the SLE Disease Activity Index (SLEDAI)[31]. Fatigue was measured according to the Fatigue Severity Scale (FSS)[13]. The FSS is a 9 item questionnaire where each item is scored from 1 to 7, and the FSS score is the mean of the 9 statement score. It evaluates the impact of fatigue on activities of daily living.

MRI scans of the brain were performed using a 0.5 T magnet (Gyroscan T5 II; Philips, Eindhoven, The Netherlands) in 52 patients. A sagittal T1 weighted (WI) sequence [520/20/2 (repetition time/echo time/excitations)] with 6.0/0.6 mm (slice thickness/interspace) followed by an axial T2WI SE [2000/20/90 (repetition time/echo time)] with 5.0/0.5 mm (slice thickness/interspace) was performed on the entire brain. A circular, transmit-receive head coil with matrix of 256 × 256 and a field of view of 250 mm was used. One neuroradiologist (EAJ), blinded to clinical data, read all images. An infarct was defined as an area with low T1 or proton density and high T2 signal intensities, > 15 mm.

Routine hematological, biochemical, and immunological tests including diabetes mellitus and thyroid function were performed at the hospital's laboratory. Antinuclear antibodies (ANA) and subspecificities were determined by ELISA technique. Analysis for anticardiolipin of IgG and IgM isotypes was performed by a commercial ELISA according to the manufacturer (Shield, Dundee, UK). Values > 30 GPL and 30 MPL U/ml were considered positive. Tests for anti-$ß_2$-glycoprotein I (anti-$ß_2$-GPI) of IgG and IgM isotypes were performed by ELISA (IMTEC Immundiagnostica, Berlin, Germany). Values > 7 U/ml were considered positive according to the manufacturer's recommendations.

Cytokine assays. Whole blood samples were collected between 7 and 8 AM and allowed to clot in icewater. After centrifugation, serum was immediately frozen and stored in small aliquots at –70°C, which were only allowed to thaw once upon analysis.

IFN-α, TNF-α, IL-2, IL-6, and IL-10 were measured by commercially available competitive enzyme immunoassay kits (Accucyte®, Cytimmune Sciences Inc., College Park, MD, USA) according to the manufacturer. These assay methods measure total cytokine in biological fluids, both bound and unbound. The sensitivities and range of detection for the different assays were as follows: IFN-α: sensitivity 0.391 ng/ml; range 0.391–400 ng/ml. TNF-α, IL-2, IL-6, and IL-10: sensitivity 0.195 ng/ml; range 0.195–50.0 ng/ml. TGF-ß was measured by Biosource TGF-ß1 ELISA kit (BioSource International, Camarillo, CA, USA) according to recommendations from the manufacturer. The sensitivity was 2 pg/ml and range 2–2000 pg/ml.

Statistics. In most instances data were normally or near normally distributed, and parametric statistics therefore applied for calculation. Results are thus presented as means. Unpaired t test (2 tailed) or analysis of variance was used to test differences between 2 or more groups of quantitative data, and chi-square for categorical data. Simple or multiple regression with FSS as dependent variable was used to test associations between fatigue and quantitative variables. Using relevant nonparametric statistics did not alter the results.

RESULTS

If considered present when the Fatigue Severity Scale score is ≥ 3[10], 45 of the patients with SLE (79%) reported fatigue. The frequency distribution of the FSS scores is shown in Figure 1, while the mean, standard deviation, and ranges are given in Table 1 together with the results of the SLEDAI, erythrocyte sedimentation rate (ESR), TNF-α, IL-2, IL-6, IL-10, TGF-ß, and IFN-α. A mean SLEDAI of 5.8 (± 5.4) reflects moderate disease activity, and is in accordance with the observation of relatively mild disease in Scandinavian patients with SLE[32]. Results of selected qualitative variables like anti-dsDNA, complement factors C3 and C4, aCL, and a$ß_2$-GPI are shown in Table 2.

Neurological examination revealed clinical evidence of stroke in 5 patients (9%), epilepsy in 3 (5%), while one patient had a myelopathy. Fourteen (27%) of the 51 patients that agreed to nerve conduction velocity (NCV) studies had neurophysiological signs of peripheral neuropathy. One patient had a bilateral carpal tunnel syndrome, without evidence of peripheral neuropathy.

MRI scans (Table 2) revealed cerebral infarcts in 9 SLE patients (17%). Five patients (10%) had a single large infarct, and 4 patients (8%) had multiple small infarcts. Only one patient with cerebral infarcts on MRI scanning had abnormal neurological findings indicating a stroke.

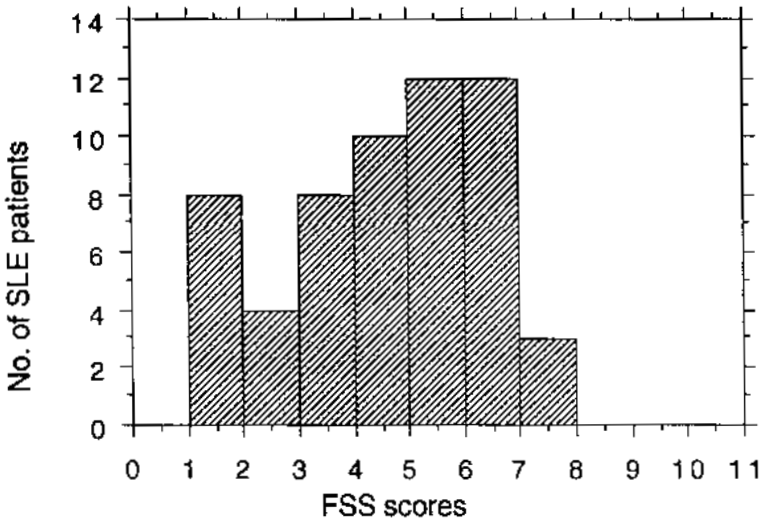

Figure 1. Frequency distribution of scores on the Fatigue Severity Scale (FSS) in 57 patients with SLE.

Table 1. Selected quantitative variables in 57 patients with systemic lupus erythematosus, showing fatigue scores, disease activity, erythrocyte sedimentation rate (ESR), and cytokine concentrations in serum.

Variable	Mean ± SD	Range	Normal Range
FSS	4.6 ± 1.8	1–7	< 3
SLEDAI	5.8 ± 5.4	0–29	
ESR (mm/h)	23.4 ± 19.2	1–87	< 20
TNF-α (ng/ml)	0.5 ± 6.4	0.2–29.9	0.5–6.5*
IL-2 (ng/ml)	2.9 ± 2.3	0.2–8.6	0.5– 7.0*
IL-6 (ng/ml)	1.5 ± 1.2	0.2– 4.6	0.5– 7.0*
IL-10 (ng/ml)	7.5 ± 8.5	0.2–50.0	0.5–5.0*
TGF-ß (ng/ml)	87.8 ± 28.7	17.2–154.0	NA
IFN-α (ng/ml)	34.1 ± 28.9	0.2–190.8	NA

*According to the manufacturer Cytimmune Sciences. FSS: Fatigue Severity Scale. NA: Data not available. SLEDAI: SLE Disease Activity Index; TNF-α: tumor necrosis factor-α; IL-2: interleukin 2; TGF-β: transforming growth factor-β; IFN-α: interferon-α.

Table 2. Selected qualitative variables in 57 patients with systemic lupus erythematosus.

Variable	Normal (%)	Abnormal (%)
Anti-dsDNA	36 (63.2)	21 (36.8)
C3 [0.84–2.15 g/l]	41 (71.9)	16 (28.1)
C4 [0.08–0.33 g/l]	52 (91.2)	5 (8.8)
aCL IgG [< 30 GPL]	51 (89.5)	6 (10.5)
aCL IgM [< 30 MPL]	54 (94.7)	3 (5.3)
Anti-ß$_2$-GPI IgG [< 7 U/ml]	22 (38.6)	35 (61.4)
Anti-β$_2$-GPI IgM [< 7 U/ml]	43 (75.4)	14 (24.6)
Cerebral infarcts, MRI [No. of subjects = 52]	43 (82.7)	9 (17.3)
Stroke, clinical findings	52 (91)	5 (9)
Peripheral neuropathy [No. of subjects = 51]	37 (73)	14 (27)

Associations between FSS and other variables. There were no associations between FSS scores and age, sex, hypertension, or use of beta blockers or thyroxine-Na. A near-significant association between lower hemoglobin values and higher FSS scores was found ($y = 7.8 – 0.3*x$; $R^2 = 0.06$; $p = 0.06$), and similarly patients with low C4 had higher FSS scores than those with normal C4 (FSS scores 6.0 and 4.4, respectively; $p = 0.05$). Disease duration, number of months taking prednisolone, antimalarials, azathioprine, and number of months without medication for SLE did not influence FSS. This also applied to SLEDAI, ESR, creatinine clearance, and abnormal urine findings. Similarly there were no associations between FSS scores and positive ANA or subspecificities like anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, C3, aCL IgG and IgM, anti-ß$_2$-GPI IgG and IgM, or TNF-α, IL-2, IL-6, IL-10, TGF-ß, and IFN-α.

There was no difference in FSS scores between patients with or without cerebral infarcts observed on MRI, or between those with or without clinical signs of cerebral stroke. Similarly, if all CNS manifestations were considered as one group, these patients did not have higher fatigue scores than those without CNS manifestations.

DISCUSSION

We found that the magnitude and prevalence of fatigue in patients with SLE in this study are in accordance with other comparable studies[7,10,13,16], showing that almost 4/5 patients report this to be a significant complaint. Fatigue is therefore a prominent and to some degree disabling feature of NPSLE. We believe that fatigue may cause longstanding sick leave or other disability problems related to work and daily life in patients with SLE. This problem may have been given relatively little attention in the past, compared to other features of the disease.

We also found that disease activity in SLE does not influ-

ence fatigue. This is in agreement with our clinical experience, where SLE patients report severe fatigue despite apparent complete remission. The reason for the observed associations between fatigue and disease activity in other studies may well be, as argued by Tench, *et al*[16], that instruments other than the SLEDAI often include fatigue as a component score. This leads to circular argumentation. Accordingly, studies applying the SLEDAI have not found a clear-cut association with fatigue[9,17].

Except for a possible association between low C4 and fatigue, we did not find other laboratory evidence of a link between inflammatory activity and fatigue. This contrasts with our general hypothesis of fatigue as a consequence of inflammation[12,18]. Similarly, autoantibody profiles including ANA and its subspecificities did not influence FSS scoring.

Cytokines are essential messenger molecules in the regulation of immunological activity. Although data are conflicting due to their different sources (cells vs serum) and methods (stimulated cells, unstimulated cytokine secretion, or mRNA expression) there is a general agreement that unstimulated serum levels of sIL-2R, IL-2, IFN-γ, TNF-α, IL-6, IL-10, and IFN-α are increased in SLE patients[20-22]. In light of infusion studies with TNF-α[25], IL-2[26], IL-6[27], and IFN-α[28] resulting in profound fatigue, or, in contrast, the immediate disappearance of fatigue following administration of anti-IL-6 receptor antibody therapy[29], as well as the cytokine aberrations observed in CFS[19,23,24], we postulated that the serum levels of these cytokines would influence fatigue in patients with SLE. This could be mediated through disruption of the blood-brain barrier or other mechanisms since it is known that peripherally derived cytokines may communicate with the brain[33]. The reportedly high plasma concentrations of TNF-α and IL-6 in patients with excessive daytime sleepiness would also favor such a hypothesis[34]. We were, however, not able to observe any association between fatigue and serum cytokine levels of TNF-α, IL-2, IL-6, IL-10, TGF-ß, or IFN-α. The explanation for this may be that much higher elevations of relevant cytokines in serum are necessary to obtain similar effects in CNS fatigue as observed in infusion studies. Such concentrations may normally not be reached in patients with SLE. Measuring cytokines in serum may therefore be the wrong place to search for the effect of cytokines on fatigue, and paracrine effects on neuronal cells of intrathecally produced cytokines may be a more relevant target for research.

A few studies[35,36] have postulated that persistently elevated aCL levels in serum may lead to subtle deterioration in cognitive function in patients with SLE. Our study, showing no association of aCL or $ß_2$-GPI antibodies with fatigue, did not support this assumption; nor did another, recent study of SLE patients from our group[37]. In fact, whereas we could show that cerebral infarcts explain cognitive dysfunction in SLE[37], the present study does not support the idea that such structural brain damage influences fatigue problems.

Concomitant diseases or complications of SLE did not affect fatigue scores, and we could not confirm any difference in fatigue between patients on or off treatment for SLE, or on treatment with thyroxine-Na or beta blockers. All patients were euthyroid even though 5 patients received thyroxine-Na substitution. Similarly, there was no difference in fatigue scores for patients on or off prednisolone, antimalarials, azathioprine, or combinations of these. This is in contrast to Tench, *et al*[16], who observed significantly higher fatigue scores in patients taking hydroxychloroquine.

There are alternative explanations for the high prevalence of fatigue that does not correlate with immunological or inflammatory variables in SLE. Psychosocial factors such as affective disorders, anxiety, sleep disturbances, poor quality of life, or chronic pain syndromes like fibromyalgia may be predictors of the phenomenon[16,17]. This is an aspect not addressed in this paper.

In summary, we confirm that the magnitude and prevalence of fatigue as evaluated by the Fatigue Severity Scale is high in patients with SLE. It has no association to disease activity or other markers of disease or inflammation, except for a tendency for anemia and low complement factor C4. Surprisingly, neither the levels of cytokines TNF-α, IL-2, IL-6, IL-10, TGF-ß, and IFN-α in serum nor aPL antibodies influence fatigue in these patients. Fatigue is a complex phenomenon, and cytokine involvement may take place intrathecally via auto or paracrine mechanisms. Alternatively, psychosocial factors may well be the dominant predictor of fatigue in patients with SLE.

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