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Fatigue in Patients with Early-Stage Systemic Lupus Erythematosus Before Receiving Corticosteroid Therapy: A Prospective Cross-Sectional Study

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Abstract

Objective: Fatigue has been intensively studied in patients with systemic lupus erythematosus (SLE). However, previous studies have mostly included patients with long-term disease who have been treated with corticosteroids. We investigated fatigue in corticosteroid-naive patients with early-stage SLE.

Methods: Forty-three SLE inpatients without neuropsychiatric SLE manifestations and 30 healthy control subjects with similar demographic characteristics participated in this study. The Profile of Mood States (POMS) was used to assess fatigue, depression and anxiety. Results of clinical, laboratory, and neurological tests were compared and their relationship with fatigue was assessed.

Results: The prevalence of fatigue did not differ between patients (n = 8, 19%) and controls (n = 6, 20%; p = 0.556), and the severity of fatigue also did not differ between groups (p = 0.590). Using multiple logistic regression analysis, we identified POMS-anxiety (OR, 1.14; 95% CI, 1.019 - 1.273, p = 0.022) as an independent risk factor for fatigue in these patients. There were no relationships between fatigue, disease activity, and concentrations of inflammatory markers.

Conclusion: Our results indicate that fatigue does not occur more frequently in corticosteroid-naive patients with early-stage SLE than in the normal population, and that fatigue may be related to anxiety.

Keywords

Systemic lupus erythematosus, Fatigue, Anxiety, Corticosteroids

Introduction

Systemic lupus erythematosus (SLE) is a chronic relapsing/remitting autoimmune disease characterized by multisystem involvement and diverse manifestations. Fatigue is the most prevalent symptom, affecting up to 90% of patients with SLE [1]; it is also the most debilitating symptom reported by patients with SLE [2]. The fatigue associated with SLE decreases patient quality of life [3-6] and reduces their ability to work [7,8]. The origin of fatigue is multifactorial and, despite its high prevalence and adverse clinical, social, and economic effects, its pathophysiological mechanisms are still unclear. There are several comorbid conditions associated with fatigue: reduced physical activity [9,10], obesity [11], sleep disturbance [12], depression [13-15], depression and anxiety syndrome [13], pain [1,15], vitamin D deficiency [16], and fibromyalgia [17]. Disease activity also seems to be a major factor associated with fatigue, although this relationship has been inconsistent in SLE patients [1,13,15,18,19]. No associations between fatigue and levels of serum cytokines such as interleukin (IL)-2, IL-6, or interferon (IFN)-α have been reported [20]. The findings of brain imaging studies investigating fatigue in SLE patients have also yielded inconsistent results. These have included negative findings from studies using magnetic resonance imaging (MRI) [20] and single-photon emission computed tomography [21] and positive findings from a study that used a semi-quantitative radiologic scale on a T-2 weighted MRI to detect the relationship between white matter hyper intensities and fatigue [22]. Although fatigue occurs in SLE patients relatively early in the disease [23], to our knowledge no reports have focused on fatigue in patients with early disease who have not yet received corticosteroid therapy.

The purpose of this study was to clarify the prevalence of, and risk factors for, fatigue in corticosteroid-naive patients with early-stage SLE. We compared fatigue between these SLE patients and healthy control participants, and assessed the association of fatigue with patient psychological health and neurological/immunological variables.

Patients and Methods

Patients and controls

The participants in this study were the same as those described

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in our previous study, which focused on neurocognitive impairment in SLE [24]. These participants were Japanese patients who were admitted to the Institute of Rheumatology at the Tokyo Women's Medical University Aoyama Hospital between 2000 and 2006, and who met all of the following criteria: 1) diagnosed with SLE based on criteria defined by the American College of Rheumatology (ACR) [25], 2) no history of corticosteroid or other immunosuppressive therapy, 3) not unable to participate in the psychiatric interview or complete the neuropsychological tests and questionnaires because of poor physical condition, 4) except for adjustment disorder, no history of major psychiatric disorders including substance abuse, and 5) no history of neurologic illness (e.g., strokes, seizures, or head injury resulting in loss of consciousness). All patients were screened for current and previous major psychiatric conditions using the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders, Non-patient Edition (With Psychotic Screening), Version 2.0 (SCID-I-NP) [26]. The study was approved by the ethics committee of Tokyo Women's Medical University. All participants gave their informed written consent.

Of the 54 corticosteroid-naive patients with SLE who were admitted during the study period, one patient declined the invitation to participate, two were excluded based on the initial SCID-I-NP interview (criterion 4), and eight could not complete the neuropsychological tests (criterion 3). As a result, data from 43 patients were available for analysis.

Thirty healthy controls were recruited from hospital staff and their relatives for neuropsychological testing. All controls were Japanese women with no history of major psychiatric disorders or neurologic illnesses as determined by the SCID-I-NP and neurologic history-related questions. The demographics of the control group (age, education level, and personality profile) were similar to those of the SLE group. Demographic, clinical, and psychological characteristics of the SLE and control groups are shown in table 1.

Assessment of fatigue, depression and anxiety

The fatigue levels of both patients and controls were evaluated using the Profile of Mood States (POMS) [27] fatigue subscale. The POMS provides scores on six separate subscales: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, and confusion. The validity and reliability of the Japanese version of the POMS have been previously confirmed [28]. The POMS fatigue subscale consists of seven items that are rated on a five-point Likert scale ranging from "not at all" (0) to "extremely" (4). Each POMS fatigue subscale has factorial integrity and can be used independently of the others [29]. Both the patients and the controls were also evaluated using the POMS depression-dejection and tension-anxiety subscales to assess their depression and anxiety, respectively. Raw scores from each subscale were converted to T-scores based on the normative data, and a T-score > 60 was considered positive. Patients also completed a questionnaire regarding fatigue using visual analog scales (VAS) for fatigue (0-100 mm, with 100 mm indicating the most severe fatigue).

Table 1: Demographic, clinical, and psychological characteristics of corticosteroid-naive SLE patients vs. healthy controls.

Variables	SLE patients (*N* = 43)	Controls (*N* = 30)	*p*
Demographics			
Age, years	28.7 (8.6)	28.1 (6.7)	0.822
Female	41/42 (97.6)	30/30 (100)	> 0.999
Education, years	13.4 (1.9)	13.3 (1.7)	0.963
Clinical charasteristics			
Disease duration, months[a]	26.1 (40.9)	NA	
Time since SLE diagnosis, months	3.2 (18.3)	NA	
Performance status[b]	0.4 (0.6)	NA	
Pain, VAS, mm	30.4 (24.0)	NA	
Fatigue, VAS, mm	33.0 (27.6)	NA	
SLEDAI-2K	11.9 (5.9)	NA	
Profile of Mood State (POMS) subscales			
Tension-Anxiety	14.1 (7.1)	10.7 (5.8)	0.043[c]
Depression-Dejection	13.9 (10.2)	9.2 (7.2)	0.045[c]
Fatigue	11.0 (6.2)	10.5 (6.7)	0.590

Data are number/number assessed (%) or mean (standard deviation).

P values were determined by Fisher's exact test or Mann-Whitney U-test.

[a]Defined as the time between the onset of SLE-attributable symptoms and assessment

[b]Determined based on Eastern Cooperative Oncology Group criteria

[c]Significant variables

NA = Not Applicable

VAS = Visual Analog Scale

SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000

Clinical/health assessment

Disease duration was defined as the time between the onset of SLE-attributable symptoms and the assessment for this study. Global SLE-disease activity was evaluated using the systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) [30] at the same time as the psychological assessment or within the preceding 10 days.

Daily-living activities were evaluated using the Eastern Cooperative Oncology Group Scale of Performance Status. Patients also completed a questionnaire regarding pain using a VAS (0-100 mm, with 100 mm being the most severe pain). Sleep disturbance levels were derived by summing the scores of three subscales for insomnia (initial, middle, and delayed insomnia, each value: 0-2) from the 17-item Hamilton Depression Rating Scale.

Immunological/neurological markers

Anti-ds-DNA antibodies and serum complement CH50 were measured as markers of disease activity. Based on published reports regarding fatigue in SLE [23,31,32] the following potentially relevant laboratory and neurologic variables were selected: antiphospholipid antibodies; cerebrospinal fluid (CSF) and serum concentrations of IL-6, IL-8, and IFN-α; the CSF immunoglobulin G [IgG] index; brain MRI images; and electroencephalograms (EEG). Of the 43 patients, 37 underwent cerebrospinal fluid tests, 41 had brain MRI, and 41 underwent EEG. These neuropsychological, laboratory, and neurological tests were completed within a week after admission and before corticosteroids or other immunosuppressive therapies were administered. Control participants completed the neuropsychological tests, but did not undergo brain MRI, EEG, or cerebrospinal fluid testing.

Statistical analyses

For the univariate analyses, the non-parametric Mann–Whitney *U*-test was used to identify differences between groups for continuous variables, and the Fisher exact test was used for categorical variables. To identify independent risk factors for fatigue in SLE patients, multiple logistic regression analysis was performed with forward stepwise variable selection. Variables from the univariate analyses with $p < 0.25$ were entered into a forward logistic regression model. Regression coefficients were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of the ORs. For all statistical analyses, p-values < 0.05 were considered statistically significant. We performed all analyses using SPSS® Statistics 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Prevalence and severity of fatigue

The prevalence of fatigue did not differ between groups (patients: 19%, n = 8; controls: 20%, n = 6; $p = 0.556$). POMS scores for fatigue also did not differ between the SLE and the control groups ($p = 0.590$, Table 1). Mean (standard deviation, SD) scores for VAS fatigue in SLE patients were 33.0 (27.6) (range; 0-96). The VAS and POMS scores for fatigue showed a strong positive correlation (r = 0.623, $p < 0.001$).

Table 2: Demographic, clinical and immunological/neurological characteristics of corticosteroid-naive SLE patients with vs. without fatigue.

Variables	Fatigue, yes (n = 8)	Fatigue, no (n = 35)	*p*
Demographics			
Age, years	31.4 (8.7)	28.1 (8.6)	0.295
Female	8/8 (100%)	34/35 (97/1%)	0.814
Education, years	13.5 (2.1)	13.4 (1.9)	0.948
Clinical characteristics			
Disease duration, months	17.1 (20.6)	28.2 (44.2)	0.407
Time since SLE diagnosis[a], months	0.0 (0.0)	3.9 (20.2)	0.114
SLEDAI-2K	14.0 (6.5)	11.4 (5.7)	0.332
Perfomance Status[b]	0.9 (0.8)	0.3 (0.5)	0.032[c]
Pain, VAS, mm	42.1 (21.4)	27.7 (24.0)	0.108
Sleep disturbance[d]	1.5 (2.0)	0.7 (1.1)	0.140
POMS-Anxiety	21.3 (8.3)	12.4 (5.8)	0.005[c]
POMS-depression	23.8 (12.0)	11.7 (8.4)	0.009[c]
Immunological/neurological markers			
Anti-DNA antibody, IU/ml, median (IQR)	32.5 (9.0 - 79.5)	102.0 (13.0 - 268.0)	0.225
CH50, U/ml, median (IQR)	12.3 (10.0 - 29.5)	24.6 (12.6 - 33.1)	0.225
Antiphospholipid antibody, positive[e]	2/8 (25.0%)	12/35 (34.3%)	0.478
Interleukin-6, pg/ml (serum), median (IQR)	2.3 (0.6 - 5.2)	3.6 (0.9 - 7.0)	0.471
Interleukin-6, pg/ml (CSF), median (IQR)	2.46 (1.2 - 6.95)	7.9 (2.8 - 11.0)	0.072
Interleukin-8, pg/ml (serum), median (IQR)	13.8 (0.0 - 50.2)	14.4 (0.0 - 62.9)	0.852
Interleukin-8, pg/ml (CSF), median (IQR)	41.5 (22.7 - 130.6)	78.0 (35.7 - 129.5)	0.537
Interferon-α, IU/l (serum), median (IQR)	0.0 (0.0 - 27.4)	0.0 (0.0 - 1.0)	0.210
Interferon-α, IU/l (CSF), median (IQR)	0.0 (0.0 - 15.5)	0.0 (0.0 - 3.0)	0.236
IgG index, positive (normal < 0.70)	0/6 (0.0%)	6/31 (19.4%)	0.561
Brain MRI, abnormal[f]	2/8 (25.0%)	4/33 (12.1%)	0.331
Electroencephalogram, abnormal	4/8 (50.0%)	14/33 (42.4%)	0.500

Data are number/number assessed (%), mean (standard deviation: SD), or otherwise stated.

P values were determined by Fisher's exact test or Mann - Whitney U-test.

[a]Time between being diagnosed with SLE based on ACR criteria (1997) for the first time and assessment.

[b]Determined using Eastern Cooperative Oncology Group criteria

[c]Significant variables

[d]Total scores from the three sleep-related items in the Hamilton Depression Rating Scale-17 items

[e]Antiphospholipid antibodies include anticardiolipin-b2-glycoprotein-I complex and lupus anticoaglant.

[f]All detected abnormalities consisted of small focal lesions (ø < 10 mm) in the white matter.

VAS = Visual Analog Scale

SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000

POMS = Profile of Mood State

IQR = Interquartile Range

CSF = Cerebrospinal Fluid

Risk factors for fatigue in SLE patients

Patients were divided into two groups according to the presence or absence of fatigue. Then, demographic, clinical, immunological/neurological variables (Table 2), and cumulative symptoms of SLEDAI-2K (Table 3) were compared between the two groups. Among these variables, scores for the following characteristics were significantly higher in patients with fatigue than in those without: performance status (p = 0.032), POMS-anxiety (p = 0.005), and POMS-depression (p = 0.009). Furthermore, pleurisy was present significantly more frequently in patients with fatigue than in those without (p = 0.037). Multiple logistic regression analysis showed that POMS-anxiety was the only independent risk factor for fatigue in SLE patients. The OR was 1.139 (95% CI, 1.019–1.273, p = 0.022; -2 log likelihood = 38.793; χ^2 = 6.290, p = 0.012; Nagelkerke R^2 = 0.293).

Discussion

Our results showed that the prevalence and severity of fatigue did not differ between patients with early-stage SLE, even when free from the potential effects of corticosteroids, and healthy controls. Since fatigue has been reported to be the most prevalent symptom, affecting up to 90% of patients with SLE [1], findings from the present study suggested that fatigue in SLE patients may be associated with long-term disease-related or treatment-related factors.

The point prevalence of fatigue in patients with SLE has been reported to vary widely [1] this prevalence varies with the definition and instruments used to assess fatigue, which are inconsistent throughout the literature. The ad hoc Committee on SLE response criteria for fatigue has recommended the use of the 9-item Fatigue Severity Scale (FSS) [33] for assessing fatigue in SLE patients [34]. The reported percentages of SLE patients experiencing clinical fatigue assessed using the FSS, the most frequently used instrument in studies on SLE-related fatigue, range from 67% to 90% [2]. The prevalence of fatigue in patients with early-stage SLE in this study was markedly lower than that reported in SLE patients in several previous studies, although we could not directly compare our results with those of earlier works because we used POMS-fatigue in our study. We used the POMS so that separate evaluations of fatigue, depression, and anxiety were possible, because the symptoms of depression overlap with those of fatigue. Furthermore, the fact that patients with severe fatigue were excluded may have reduced the prevalence rate.

In the present study, fatigue was not independently related to the level of disease activity or any immunological/neurological markers, although most patients had overall disease activity (SLEDAI-2K ≥ 6 in 88.4%) that was moderate or high and free from the potential influence of medication. This finding was consistent with the findings of several previous studies that showed weak or no association between fatigue

Table 3: Cumulative symptoms of SLEDAI-2K in corticosteroid-naive SLE patients with vs. without fatigue.

Variables	Fatigue, yes (n = 8)	Fatigue, no (n = 35)	*p*
SLEDAI-2K items[a]			
Visual disturbance	0/8 (0%)	1/35 (3%)	> 0.999
Vasculitis	0/8 (0%)	1/35 (3%)	> 0.999
Arthritis	7/8 (88%)	19/35 (54%)	0.088
Myositis	0/8 (0%)	1/35 (3%)	> 0.999
Urinary casts	1/8 (13%)	7/35 (20%)	0.533
Hematuria	1/8 (13%)	6/35 (17%)	0.612
Proteinuria	1/8 (13%)	7/35 (20%)	0.533
Pyuria	2/8 (25%)	4/35 (11%)	0.308
New rash	3/8 (38%)	17/35 (49%)	0.434
Alopecia	1/8 (13%)	6/35 (17%)	0.612
Mucosal ulcers	2/8 (25%)	1/35 (3%)	0.084
Pleurisy	3/8 (38%)	2/35 (6%)	0.037[b]
Pericarditis	0/8 (0%)	2/35 (6%)	> 0.999
Low complement	6/8 (75%)	31/35 (89%)	0.308
Increased DNA binding	6/8 (75%)	30/35 (86%)	0.388
Fever	1/8 (13%)	10/35 (29%)	0.241
Thrombocytopenia	1/8 (13%)	3/35 (9%)	0.576
Leukopenia	4/8 (50%)	11/35 (31%)	0.275

Data are number/number assessed (%).

P values were determined by Fisher's exact tests.

[a]Significant variables

[b]Other SLEDAI-2K symptoms (seizure, psychosis, organic brain syndrome, cranial nerve disorder, lupus headache, and cerebrovascular accident) were not found in any patient.

SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000

and disease activity [1,13,15,18]; although some studies have shown a significant positive association between these factors [19]. There is abundant evidence that many patients with chronic fatigue syndrome (CFS) may suffer from autoimmune response [35]. Thus, future long-term study may serve an important clue to study the pathogenesis of CFS.

Among psychological variables, depression has been consistently reported to be strongly associated with fatigue in SLE patients [14,15,19,22,36]; however, in our study the association between fatigue and depression did not reach significance after multivariate analysis. Instead, our multivariate analysis revealed an independent relationship between fatigue and anxiety. Anxiety alone has not previously been shown to be associated with fatigue in SLE patients, although the depression and anxiety complex assessed using the hospital anxiety and depression scale (HADS) has been reported to have an association with fatigue [13]. Furthermore, several studies have suggested an indirect association between fatigue and anxiety through evaluation of psychosocial variables such as helplessness [19], perceived lack of social support [15], or work disability [37,38]. In addition, most patients in this study were female. Females are at greater risk for depression and anxiety-related disorders in the general population [39].

The strengths of our study were the early-stage, corticosteroid-naive SLE population, comprehensive collection of psychological and biological data, and the use of multivariate statistical analyses to identify predictive factors for fatigue in patients with SLE. However, our study had several limitations. First, in this study we used the POMS subscale to evaluate fatigue, although this instrument had not been previously used for this purpose in the study of SLE [2]. Therefore, we could not directly compare the prevalence of fatigue found in our study to that found in previous studies. Second, this study lacked prospective long-term analysis, which could have been helpful for defining predictors of fatigue (e.g., comparison of levels of fatigue before and after corticosteroid administration). Third, because of its small sample size, the statistical power of our study to identify factors that predict fatigue was relatively low. Finally, because the results in our study were obtained from a limited population of relatively young female patients with early SLE, the findings may not be applicable to all SLE patients, particularly male or with longer disease duration.

In conclusion, the results of our study suggest that fatigue does not occur more frequently in corticosteroid-naive patients with early-stage SLE than in healthy controls, and that fatigue is associated with anxiety. There were no relationships between fatigue, disease activity, and inflammatory markers, even without the potential effects of corticosteroids. Further follow-up studies using larger sample sizes are needed.

Competing Interest

The authors declare that they have no competing interests.

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