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S. Yilmaz-Oner[1] · B. Ilhan[2] · M. Can[1] · F. Alibaz-Oner[1] · O. Polat-Korkmaz[2] · G. Ozen[1] · G. Mumcu[3] · H. M. Kremers[4] · S. Tuglular[5] · H. Direskeneli[1]

[1] School of Medicine, Department of Rheumatology, Marmara University, Pendik Istanbul, Turkey
[2] School of Medicine, Marmara University, Istanbul, Turkey
[3] Faculty of Health Sciences, Department of Health Management, Marmara University, Istanbul, Turkey
[4] College of Medicine, Department of Health Sciences Research, Mayo Clinic, Rochester, USA
[5] School of Medicine, Department of Nephrology, Marmara University, Istanbul, Turkey

Fatigue in systemic lupus erythematosus

Association with disease activity, quality of life and psychosocial factors

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease characterized by broad and variable clinical manifestations and an unpredictable disease course with remissions and exacerbations [1]. Previous studies have shown that patients with SLE have lower health-related quality of life (HRQoL) compared to healthy controls [2, 3] and patients with other chronic diseases [4]. Studies have indicated fatigue as a significant characteristic of lupus and it has been identified as an essential factor negatively affecting the quality of life of lupus patients [5, 6]. Fatigue is a very common symptom in SLE, experienced by up to 90 % of patients and described as the most disabling disease symptom by approximately 50 % [7, 8]. It was also found to be negatively correlated with both dimensions (physical and mental component scores) of HRQoL measured by the medical outcomes study short form-36 health survey (SF-36) [7].

Although it is the most prevalent complaint in patients with SLE, the cause of fatigue is still unknown. The association between disease activity and fatigue is controversial. Some studies have shown poor correlation between fatigue and disease activity [9, 10], whereas others reported an association with disease activity [11–13]. Wang et al. also suggested that fatigue was more closely associated with QoL, depression and fibromyalgia [10]. The other reported factors associated with SLE-related fatigue were anxiety, sleep disturbance, physical inactivity and lack of social support [9, 12–14].

A biological perspective on cognitive impairment, depression and fatigue in SLE has also been investigated [15]. Interleukin 1 (IL-1), IL-6 and tumor necrosis factor alpha (TNF-alpha) are proinflammatory cytokines implicated in chronic fatigue and all of these are present in chronic inflammatory state of SLE [16]. Proinflammatory cytokines have been indicated to promote oxidative and nitrosative stress with ending production of damage-associated molecular pattern molecules (DAMPS) that engage with Toll-like receptors (TLR) [17]. The interaction of DAMPS and TLR results in symptoms of extreme fatigue in SLE patients. Additionally, antibodies to N-methyl D-aspartate receptors (anti-NMDAR) and ribosomal *P* (anti-*P*), which are brain-reactive autoantibodies implicated in SLE, have been shown to mediate mechanisms for transient cognitive or mood disturbances. Interferon α is another important cytokine that plays a role in disease pathogenesis and neuropsychological symptoms of SLE, such as fatigue, depression and seizures [15].

SLE-related fatigue disrupts patients' normal daily life, affects work and social activities and 81 % of patients indicated that they are not adequately supported in the management of SLE-related fatigue by healthcare services [18]. In routine daily practice, objective parameters are used for the evaluation of patient disease activity and treatment efficacy; however, silent burdens of the disease (e.g. pain, fatigue, anxiety, depression and fibromyalgia) are usually not addressed in patient health care management planning [19]. Fatigue is an individual, subjective and heterogeneous symptom and therefore is difficult to measure. Several scales have been developed for quantification of its measurement, such as the fatigue severity scale (FSS) [20] and the multidimensional assessment of fatigue (MAF) scale [21].

Cultural and religious aspects are important variables that may play role in expression of fatigue [22]. Patient coping strategies with disease can be related with their beliefs, perceptions and cultural background. Hifinger et al. showed that the country of residence has an important influence on the level of fatigue and they also indicated that fatigue levels were variable across countries. They indicated that the data about fatigue cannot be transferred between different countries and patients in high-income countries or in countries with higher level of human development had higher levels of

S. Yilmaz-Oner and B. Ilhan contributed equally to the study

Table 1 General features of the patient and control groups

		SLE	Controls
Sex (*n*, %)	Female	95 (95.9)	40 (56.3)
Age ± SD (years)		43.3 ± 12.2	43.2 ± 12.1
Education (*n*, %)	Primary school and below	60 (60.6)	41 (57.7)
	College or above	39 (39.4)	30 (42.3)
Smoking (*n*, %)	Smoker	16 (16.5)	26 (36.6)
	Non-smoker	78 (80.4)	42 (59.1)
	Ex-smoker	3 (3)	3 (4.3)
Disease duration ± SD (years)		7.8 ± 5.3	–
Disease activity (PGA, *n*, %)	Active	37 (48.1)	–
	Inactive	40 (51.9)	–
SLEDAI score, median(range)		0 (0–16)	–

SLE systemic lupus erythematosus, *PGA* physician's global assessment, *SLEDAI* systemic lupus erythematosus disease activity index

fatigue than patients from other countries [23]. Burgos et al. studied fatigue and its relationship between disease activity and damage in four ethnic groups: Texas Hispanics, Puerto Rican Hispanics, African Americans and Caucasians and they reported that Caucasian ethnicity was associated with higher levels of fatigue [24].

Fatigue has not been systematically studied in Turkish patients with SLE before and the purpose of this study was to examine which disease-related and non-disease features may explain the presence of SLE-related fatigue in our patient cohort.

Material and methods

From March 2011 to September 2012, a total of 99 consecutive patients (95 women and 4 men) with SLE followed in Marmara University Rheumatology outpatient clinics and 71 randomly selected healthy controls (40 women, 31 men) who did not have any chronic diseases and matched with patients in terms of age and comorbidities were recruited to this cross-sectional study. Due to the possibility of being a confounding factor, SLE patients and controls with comorbid chronic diseases, such as hyperthyroidism, hypothyroidism, diabetes mellitus, Addison's disease and malignancies within the last 5 years were excluded. Patients with SLE and overlapping features with other connective tissue diseases were also excluded according to the patient follow-up records. The study was approved by the local ethics committee and all participants gave written informed consent. All patients fulfilled four or more of the American College of Rheumatology (ACR) 1997 updated and revised classification criteria for SLE [25]. The physician of each patient completed a checklist containing the 19 neuropsychiatric syndromes described by the ACR to classify patients as neuropsychiatric systemic lupus erythematosus (NPSLE) or non-NPSLE. Demographic data including age, sex, educational status, smoking status and clinical information, a complete medical history, physical examination, disease duration, immunological and laboratory tests and disease activity according to physician's global assessment (PGA) and the SLE disease activity index (SLEDAI) score were recorded during the enrolment. The SLEDAI score ranges between 0–105 where 0 means no activity, 1–5 mild activity, 6–10 moderate activity, 11–19 high activity and ≥20 means very high activity [26]. The PGA score ranging from 0–3 was also used to evaluate disease activity. A PGA score of "0" means inactive, "1" mild, "2" moderate and "3" means high disease activity. We also evaluated all of the participants for fatigue, anxiety-depression and health-related quality of life (HRQoL). To assess fatigue and HRQoL, the participants were asked to complete two questionnaires, the SF-36 (ranging from 0–100) [7] and the MAF scale (range 0–50) [21]. The MAF is a self-administered questionnaire and assesses the degree of fatigue by employing 16 items using a numeric rating scale (NRS). It evaluates 3 dimensions of fatigue over the past week: severity and distress (items 1–3), impact on daily living activities (items 4–14) and timing (items 15–16). The scores for 15 items are transformed into a score from 0 (no fatigue) to 50 (severe fatigue) [21].

The hospital anxiety and depression scale (HADS) was used to assess depression and anxiety symptoms of participants [27]. The questionnaire contains 14 items, scored from 0 to 3. It comprises two sets of seven questions, aiming to detect depressive and anxiety states. A score ≥8 point was accepted as the presence of anxiety and depression in this study.

Statistics

Statistical analysis was performed using the Statistical Package for Social Science 17.0 (SPSS). Data are presented as frequencies (%), means and standard deviations (SD). The mean MAF scores of two groups were compared using Student's t-test. Spearman's coefficient for non-parametric and Pearson's coefficient for parametric data were computed. Variables that were significant in univariate analysis were included in a multivariate linear regression model. All *p*-values less than 0.05 were considered statistically significant.

Results

A total of 99 patients and 71 controls were included in the study. The mean (SD) ages of patients and controls were 43.3 ± 12.2 years and 43.2 ± 12.1 years ($p > 0.05$), respectively. The mean (SD) disease duration was 7.8 ± 5.3 years. The educational levels and smoking status of participants are summarized in **Table 1**. The sociodemographic characterization of the two groups showed no significant differences with regard to age, gender and educational status. The numbers of smokers were significantly lower in the patient group. The disease activity was recorded in 77 patients according to PGA and 37 (48.1 %) were active. The median

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Fatigue in systemic lupus erythematosus. Association with disease activity, quality of life and psychosocial factors

Abstract

Objective. The aim of the study was to determine which disease-related factors and non-disease features can explain the presence of systemic lupus erythematosus (SLE)-related fatigue in Turkish patients.

Methods. This cross-sectional study was carried out with 99 SLE patients and 71 healthy controls. To assess fatigue and health-related quality of life (HRQoL) the participants were asked to complete two questionnaires: the short form-36 health survey (SF-36) and the multidimensional assessment of fatigue (MAF) scale. Anxiety and depression of participants were assessed by the hospital anxiety and depression scale (HADS).

Results. A total of 99 patients (female/male 95/4) and 71 controls (female/male 40/31) were studied. The mean age and standard deviation (±SD) of patients and controls were 43.3 ± 12.2 years and 43.2 ± 12.1 years, respectively. The mean (SD) disease duration was 7.8 ± 5.3 years and median SLE disease activity index (SLEDAI) score was 0 (range = 0–16). The level of fatigue was higher in patients compared to controls with mean MAF scores of 24.7 ± 12.2 and 12.8 ± 9.9 ($p < 0.001$), respectively. The HADS-D and HADS-A scores were also significantly higher in SLE patients (6.6 ± 4.3 vs. 3.6 ± 2.9, $p < 0.001$ and 7.2 ± 4 vs. 4.9 ± 4, $p = 0.007$, respectively). There were no significant associations between the MAF and SLEDAI scores ($r = 0.05$, $p = 0.63$) but MAF scores positively correlated with age, HADS-A and HADS-D scores and negatively correlated with physical component summary (PCS), mental component summary (MCS) and each domain of SF-36 except role emotional in SLE patients.

Conclusion. Fatigue is an important factor influencing patient daily life independent from disease activity in our study. The SLE patients with severe fatigue should also be assessed for other possible underlying causes such as anxiety, depression and poor quality of life.

Keywords

Systemic lupus erythematosus · Fatigue · Quality of life · Anxiety · Depression

Fatigue bei systemischem Lupus erythematodes. Assoziation mit Krankheitsaktivität, Lebensqualität und psychologischen Faktoren

Zusammenfassung

Ziel. Ziel der Studie war es zu bestimmen, durch welche krankheitsbedingten Faktoren und nicht krankheitsbedingten Merkmale das Vorliegen einer durch Lupus erythematodes (SLE) hervorgerufenen Fatigue bei türkischen Patienten erklärt werden kann.

Methoden. Diese Querschnittsstudie wurde mit 99 SLE-Patienten und 71 gesunden Kontrollpersonen durchgeführt. Um Fatigue und gesundheitsbedingte Lebensqualität (HRQoL) zu untersuchen, wurden die Teilnehmer gebeten, 2 Fragebögen auszufüllen: den Short-Form(SF)-36 Fragebogen zum Gesundheitszustand und die Multidimensional Assessment of Fatigue (MAF) Scale. Angst und Depression der Teilnehmer wurden mittels der Hospital Anxiety and Depression Scale (HADS) untersucht.

Ergebnisse. Insgesamt wurden 99 Patienten (95 weiblich, 4 männlich) und 71 Kontrollpersonen (40 weiblich, 31 männlich) untersucht. Das mittlere Alter (± Standardabweichung [SD]) der Patienten und Kontrollpersonen betrug 43,3 ± 12,2 bzw. 43,2 ± 12,1 Jahre. Die mittlere (± SD) Krankheitsdauer lag bei 7,8 ± 5,3 Jahren und der mediane Score des SLE-Krankheitsaktivitätsindex („SLE disease activity index", SLEDAI) betrug 0 (Range: 0–16). Der Fatigue-Wert war bei den Patienten höher als bei der Kontrollgruppe mit einem mittleren MAF-Score von 24,7 ± 12,2 bzw. 12,8 ± 9,9 ($p < 0,001$). Die HADS-D- und HADS-A-Scores waren ebenfalls signifikant höher bei SLE-Patienten (6,6 ± 4,3 vs. 3,6 ± 2,9 [$p < 0,001$] bzw. 7,2 ± 4 vs. 4,9 ± 4, [$p = 0,007$]). Es gab keine signifikante Assoziation zwischen den MAF- und SLEDAI-Scores ($r = 0,05$; $p = 0,63$), jedoch korrelierten die MAF-Scores positiv mit dem Alter, den HADS-A- und HADS-D-Scores sowie negativ mit der Physical Component Summary (PCS), der Mental Component Summary (MCS) und jeder Domäne des SF-36-Fragebogens mit Ausnahme der emotionalen Rollenfunktion.

Schlussfolgerung. Fatigue ist ein wichtiger Faktor, der das Alltagsleben der Patienten in unserer Studie unabhängig von der Krankheitsaktivität beeinflusst. SLE-Patienten mit schwerer Fatigue sollten auch auf andere möglicherweise zugrunde liegenden Ursachen wie Angst, Depression oder schlechte Lebensqualität untersucht werden.

Schlüsselwörter

Systemischer Lupus erythematodes · Fatigue · Lebensqualität · Angst · Depression

SLEDAI score was low (range = 0–16) (**Table 1**).

The level of fatigue was higher in patients than controls and mean MAF scores were 24.7 ± 12.2 and 12.8 ± 9.9, respectively (**Table 2**). The mean global fatigue index (GFI) of females in the patient group was 24.9 ± 12 and in the control group 13.6 ± 10.2 ($p = 0.000$). Males in patient group also had a higher MAF score (20.75 ± 18) than the control group (11.7 ± 9.6, $p = 0.395$).

Table 2 also shows HADS-D, HADS-A, physical component summary (PCS) and mental component summary (MCS) scores for all participants. The HADS-D and HADS-A scores were also significantly higher in patients. In the SLE group 48.5 % ($n = 48$) of patients were depressive and 28.3 % ($n = 28$) were anxious, whereas in the controls 11.3 % ($n = 8$) were depressive and 17 % ($n = 12$) were anxious with a statistically significant difference ($p < 0.001$). Mean MAF score of patients with the education level of primary school and below was 26.32 ± 12.43 and the other group with higher education level had a MAF score of 22.43 ± 11.59 ($p = 0.122$).

Table 2 Mean fatigue, quality of life, anxiety-depression scores of patients and controls

	SLE	Controls	*p*
MAF (mean ± SD)	24.7 ± 12.2	12.8 ± 9.9	<0.001
MCS (mean ± SD)	41.4 ± 10.0	49.0 ± 8.2	<0.001
PCS (mean ± SD)	38.3 ± 10.7	51.0 ± 6.9	<0.001
HADS-D (mean ± SD)	6.6 ± 4.3	3.6 ± 2.9	<0.001
HADS-A (mean ± SD)	7.2 ± 4.0	4.9 ± 4.0	0.007

SLE systemic lupus erythematosus, *MAF* multidimensional assessment of fatigue, *MCS* mental component summary, *PCS* physical component summary, *HADS-D* hospital anxiety and depression scale-depression, *HADS-A* hospital anxiety and depression scale-anxiety, *SD* standard deviation

Table 3 Multidimensional assessment of fatigue scores in patients

Groups	Subgroups	*n* (%)	MAF scores	*p*-value
Sex	Female	95 (96)	24.9 ± 12.0	0.502
	Male	4 (4)	20.7 ± 18.0	
Smoking	Smoker	16 (16.5)	25.6 ± 14.3	0.721
	Non-smoker	81 (83.5)	24.2 ± 11.8	
[a]Depression	Depressive	48 (49)	30.3 ± 11.3	<0.001
	Non-depressive	50 (51)	19.2 ± 10.4	
[a]Anxiety	Anxious	28 (28.6)	30.5 ± 12.7	0.002
	Non-anxious	70 (71.4)	22.3 ± 11.2	
[b]Disease activity (PGA)	Inactive	40 (51.9)	22.0 ± 11.9	0.222
	Active	37 (48.1)	25.5 ± 12.6	

[a]Patients with a score of ≥8 points were accepted as anxious and depressive
[b]*PGA* physician's global assessment scores ranging from 0–3 was used to evaluate disease activity. PGA score of "0" means inactive, "1" mild, "2" moderate and "3" means high disease activity
MAF multidimensional assessment of fatigue

Table 5 Correlations between control multidimensional assessment of fatigue scores and SF-36 subdomains

	PF	RP	BP	GH	VT	SF	RE	MH
r-value	–0.595	–0.498	–0.748	–0.617	–0.602	–0.420	–0.193	–0.467
p-value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.058	0.0001

PF physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health

The GFI of participants were compared in each group with regard to sex, smoking status, physiological status and also disease activity for patients. It was significantly higher in depressive and anxious patients (**Table 3**) and significantly higher in smokers (15.8 ± 10.5 vs. 10.2 ± 9, $p < 0.02$) and anxious (19.6 ± 10.5 vs. 11.4 ± 9.3, $p < 0.008$) healthy controls.

The mean MAF scores positively correlated with age, HADS-A and HADS-D scores and negatively correlated with PCS, MCS and each domain of SF-36 except role emotional in patients (**Table 4**). There was no significant association between the MAF and SLEDAI scores ($r = 0.050$, $p = 0.63$). On the other hand a positive correlation was observed between MAF scores and HADS-A ($r = 0.302$, $p = 0.01$) and HADS-D ($r = 0.300$, $p = 0.011$) scores of healthy controls and a negative correlation between MAF scores and PCS ($r = –0.477$, $p = 0.0001$), MCS ($r = –0.408$, $p = 0.0001$) and each domain of SF-36 except role emotional (**Table 5**).

The statistically significantly correlated variables with MAF scores from **Table 4** were included in the multiregression analysis and we have seen that the strongest determining parameters of fatigue were PCS and MCS ($R^2 = 0.54$, $p < 0.05$).

Table 4 Correlations between patient multidimensional assessment of fatigue scores and age, disease duration, disease activity according to SLEDAI, HADS, SF-36

	r value	*p* value
Age	0.251	0.01
Disease duration	0.198	0.052
SLEDAI	0.050	0.63
HADS-A	0.411	0.0001
HADS-D	0.488	0.0001
PCS	–0.719	0.0001
MCS	–0.314	0.002
Physical functioning	–0.595	0.0001
Role physical	–0.498	0.0001
Bodily pain	–0.748	0.0001
General health	–0.617	0.0001
Vitality	–0.602	0.0001
Social functioning	–0.420	0.0001
Role emotional	–0.193	0.058
Mental health	–0.467	0.0001

SLEDAI systemic lupus erythematosus disease activity index, *HADS-A* hospital anxiety and depression scale-anxiety, *HADS-D* hospital anxiety and depression scale-depression, *PCS* physical component summary, *MCS* mental component summary

Discussion

Fatigue is a subjective symptom which is difficult to assess and manage during the disease course of SLE patients. Clinical assessments by physicians generally include objective disease activity and damage scales but patient perceptions of disease burden also include coexisting factors, such as fatigue, fibromyalgia, anxiety and depression. Fatigue is reported to be the most disabling factor by patients, therefore examining the factors associated with the levels of fatigue is important in clinical practice. In a study by Sterling et al. patients with SLE described fatigue as having an impact on multiple aspects of their life, such as social and family activities, emotions, cognition, work and activities of daily living [28].

Recently, Overman et al. studied severe fatigue in a broad range of rheumatic diseases and reported severe fatigue present in 41–57 % of patients with a single inflammatory rheumatic disease. Fatigue was least prevalent in patients with osteoarthritis and most prevalent

in patients with fibromyalgia [29]. In a study from the Netherlands, fatigue in primary Sjögren's syndrome (PSS) and SLE was examined and the authors indicated that the course of general fatigue after waking up was significantly different between the two groups. Patients with SLE reported decreasing levels of general fatigue whereas patients with PSS reported increasing levels [30]. Fatigue related to rheumatoid arthritis (RA) is also common and debilitating. Thyberg et al. investigated factors related with fatigue in patients with early RA and they observed that fatigue was significantly related with disease activity [31].

Although the median SLEDAI score of our SLE group was 0, patients with SLE were more exhausted than healthy controls in our cohort. Mean MAF scores of patients were lower than some previous studies, with MAF scores higher than 30 [32–34] in a significant subset. Low disease activity could be responsible for lower MAF scores of our patients than the previous studies. Pettersson et al. [35] showed higher levels of fatigue in patients with higher disease activity assessed by systemic lupus erythematosus activity measure (SLAM) and reported that incongruent associations between disease activity and fatigue in different studies may depend on which measures of disease activity are used. Fatigue is one of the subjective items included in SLAM and this is reported as a possible reason of positive association between fatigue and disease activity in this study [7]. In another study, measuring disease activity with both SLEDAI and SLAM in SLE patients, the authors reported an association of fatigue with disease activity as measured by the SLAM but not with the SLEDAI score [36]. In comparison with other scales utilized to measure disease activity, SLEDAI also has a shorter timeframe with 10 days and this could be a disadvantage in capturing the relationship between fatigue and disease activity. On the other hand, disease activity scores including subjective parameters could lead to overestimation of the relationship between disease activity and fatigue [7].

The MAF scores were not significantly different between smoker and non-smoker patients but it was significantly higher in smoking healthy controls. In a study from Sweden, fewer individuals were smokers in a group consisting of controls and patients with SLE that experienced lower levels of fatigue than higher and intermediate groups [35]. The percentage of smokers was lower in our patient group than in healthy controls and in the general population of our country and this might be the cause of a discrepancy beween our results with previous studies.

Our study has pointed out that the severity of fatigue is correlated with physiological distress and HRQoL of patients. Higher levels of depression and anxiety were observed in the SLE group and HADS-A and HADS-D scores significantly correlated with the GFI. A study by Skapinakis et al. showed that unexplained fatigue and depression might act as independent risk factors for each other in general health care [37]. Gilboe et al. reported that fatigue was more strongly associated with neuropsychiatric symptoms in comparison to clinical signs and symptoms of the diseases [38]. Physiosocial distress also predicts QoL in SLE [2]; therefore, anxiety and depression may contribute to the degree of fatigue with an alternative way via worsening the QoL of patients. The nature of the disease with unpredictable flares and probability of involving multiple organ systems might be the causes of increased prevalence of anxiety and depression in SLE patients. The other factors causing anxiety and depression may be lack of knowledge about the disease, treatment and expected outcomes of SLE [39]. In our study, there were no significant differences between MAF scores of patients with different educational levels. Fonseca et al. showed higher fatigue scores in patients with lower education and concluded that lower education may affect a patient's ability to understand the course of the disease and treatment [40]. Anxiety and depression are included among the neuropsychiatric lupus syndromes by ACR [41] and we suggest that psychiatric assessment of patients with severe fatigue would be useful to reveal possible confounding mood disorders and/or neuropsychiatric lupus.

Fatigue severity correlated with summary domains of SF-36; physical and mental components and all subscales of the questionnaire except role emotional in our study. This correlation suggests that there is a relationship between reduced QoL and the degree of fatigue in SLE, as indicated by Bruce et al. and Tench et al. [42, 43]. The decreased HRQoL may be an outcome or predictor of fatigue in SLE patients. It is also possible that other causes, such as psychosocial factors, fibromyalgia, sleep disorders, helplessness, abnormal-illness behavior may be associated with poor QoL in SLE patients. However, in this study it is difficult to determine the etiology of fatigue in SLE clearly due to its design and limitations. We have not evaluated our patients for all possible confounding factors, such as social support provided to the patient, drugs in SLE treatment, fibromyalgia, sleep disturbance and pain. The other limitation was its cross-sectional design and without a follow-up of our patients over the disease course for flares and their fatigue severity during these exacerbations.

Most of the studies about fatigue in patients with SLE have been done in western countries and very few from developing countries. If we consider cultural differences, research from developing countries would be helpful to reveal ethnic differences. Future research in this field should aim at finding instruments covering all related dimensions of fatigue in patients with SLE. Furthermore, the influence of disease on variations of fatigue levels during the day should be the subject of future investigations to be able to understand the underlying pathophysiological mechanisms of fatigue.

As a conclusion, although our study group has low disease activity, patient fatigue severity was higher than the healthy controls. Starting from this point of view, we suggest that fatigue should be considered as an important factor influencing patient daily life independent of disease activity and patients with severe fatigue should be assessed for possible underlying causes, such as anxiety and/or depression and poor QoL.

Corresponding address

Dr. S. Yilmaz-Oner, MD
School of Medicine, Department of Rheumatology, Marmara University
34890 Pendik Istanbul, Turkey
sibely113@gmail.com

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Compliance with ethical guidelines

Conflict of interests. S. Yilmaz-Oner, B. Ilhan, M. Can, F. Alibaz-Oner, O. Polat-Korkmaz, G. Ozen, G. Mumcu, H.M. Kremers, S. Tuglular and H. Direskeneli state that they have no competing interest.

All studies on humans described in this manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current revised form). Informed consent was obtained from all patients included in the study.

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Nocebo-Effekt:
Verursacht teures Scheinmedikament stärkere Nebenwirkungen als ein günstiges?

Sagt man Patienten, dass ein bestimmtes Medikament Nebenwirkungen hervorrufen kann, setzen diese häufig auch ein – selbst wenn es sich um ein wirkstofffreies Scheinmedikament handelt. Dieser sogenannte Nocebo-Effekt wird noch verstärkt, wenn die Patienten Wertinformationen über das vermeintliche Medikament erhalten. Ein teures Scheinmedikament verursacht im Test stärkere Nebenwirkungen als ein günstiges. Wissenschaftler des Universitätsklinikums Hamburg-Eppendorf (UKE) haben diese Zusammenhänge jetzt in einer Studie untersucht; ihre Ergebnisse erscheinen am Freitag im renommierten Fachmagazin Science. Zurückzuführen ist dieses Phänomen auf die Erwartungshaltung der Patienten, die sich mit bildgebenden Verfahren sogar darstellen lässt. „Bei Erwartungseffekten ist das modulierende Schmerzsystem von großer Bedeutung. Erwartungen, die im Frontalhirn entstehen, können über das modulierende Schmerzsystem die Verarbeitung von schmerzhaften Reizen in tieferen Regionen des Nervensystems wie dem Hirnstamm oder dem Rückenmark beeinflussen", erläutert Alexandra Tinnermann, Wissenschaftlerin im Institut für Systemische Neurowissenschaften des UKE. Um das modulierende Schmerzsystem unter negativen Erwartungen untersuchen zu können, haben sie eine neue Methode der funktionellen Magnetresonanztomographie (fMRT) angewandt. „Wir konnten in unserer Untersuchung zeigen, dass negative Erwartungen Auswirkungen auf drei wichtige Areale des modulierenden Schmerzsystems – auf Frontalhirn, Hirnstamm und Rückenmark – haben."

Placebo- und Nocebo-Effekt

In klinischen Studien berichten Patienten, die in der Placebo-Gruppe sind und dementsprechend ein Medikament ohne Wirkstoff erhalten haben, häufig von Nebenwirkungen. Diese passen oft genau zu den möglichen Nebenwirkungen des eigentlichen Medikamentes. Ein Scheinmedikament kann also nicht nur zur Besserung der Symptome beitragen (Placebo-Effekt), sondern auch die Nebenwirkungen des eigentlichen Medikaments hervorrufen (Nocebo-Effekt). „In unserer Studie haben wir untersucht, wie sich Wertinformationen über ein Medikament auf den Nocebo-Effekt auswirken", sagt Wissenschaftlerin Tinnermann. Dazu erhielten die Probanden ein Scheinmedikament ohne medizinischen Wirkstoff. Um eine negative Erwartung zu wecken, wurde den Probanden mitgeteilt, dass das Medikament Nebenwirkungen hervorrufen kann, die zu einem erhöhten Schmerzempfinden führen. Zusätzlich zu dieser negativen Erwartung wurde eine Hälfte der Probanden darüber informiert, dass das Medikament günstig ist, die andere Hälfte, dass es teuer ist. Die Gruppe, die das teure Scheinmedikament erhalten hat, zeigte einen größeren Nocebo-Effekt – also ein höheres Schmerzempfinden – als die Gruppe, die das günstige Präparat erhalten hatte. Tinnermann: „Die Ergebnisse zeigen, dass der Wert eines Medikaments zusätzlich zu den negativen Erwartungen das Schmerzempfinden beeinflussen kann; auch die Verarbeitung von Schmerzreizen im Rückenmark wird durch diese Faktoren verändert."

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Kontakt:
Alexandra Tinnermann
Institut für Systemische Neurowissenschaften
Universitätsklinikum Hamburg-Eppendorf (UKE)
Martinistr. 52
20246 Hamburg
a.tinnermann@uke.de