Fatigue in Systemic Lupus Erythematosus: Contributions of Disordered Sleep, Sleepiness, and Depression

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ABSTRACT. ***Objective***. To clarify the role of sleep disorders, sleepiness, and depression in patients with systemic lupus erythematosus (SLE) who complain of disabling tiredness.

Methods. Patients with SLE (31 women, 4 men) with disabling tiredness were evaluated with the Epworth Sleepiness Scale (ESS) and overnight polysomnography, followed by daytime multiple sleep latency tests (MSLT) and the Beck Depression Inventory (BDI). Their polysomnography was compared with 17 healthy, asymptomatic controls.

Results. Polysomnography of the patients in comparison with healthy controls showed impaired sleep efficiency ($p < 0.02$), high arousal frequencies ($p < 0.01$), increased stage 1 sleep ($p < 0.02$), decreased stage 3/4 slow-wave sleep ($p < 0.02$), and a high percentage (77% of patients) with increased alpha-EEG non-REM sleep. In 23% of patients periodic limb movement (PLM) disorder was observed (mean PLM index 31.1 ± 15); 26% of patients had obstructive sleep apnea (mean apnea/hypopnea index 19.3 ± 10), and one patient had narcolepsy-cataplexy. Remarkably, 51% of patients were excessively sleepy on both the ESS and MSLT (mean sleep latency < 10 min). This excessive daytime sleepiness was not related to sleep restriction. There was no association between sleepiness and SLE disease features such as neuropsychiatric SLE, medications, fibromyalgia, or disease activity. As a whole, the study group reported mild to moderate depression (mean BDI = 15.8 ± 9.9). Within the group, the sleepy patients had lower BDI scores than the non-sleepy patients ($p < 0.02$), and fewer of the sleepy patients were depressed ($p < 0.04$).

Conclusion. Primary sleep disorders, sleepiness, and depression are common in tired SLE patients. Tiredness in SLE that is the result of excessive daytime sleepiness can be distinguished from tiredness of depression. Such distinctions will help identify appropriate treatment for tired patients with SLE. (First Release Oct 1 2006; J Rheumatol 2006;33:2453–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS DEPRESSION FATIGUE
SLEEP DISORDERS DISORDERS OF EXCESSIVE SOMNOLENCE

Persistent fatigue is a common symptom of systemic lupus erythematosus (SLE) and one that seriously impairs the quality of life of patients with SLE[1-3]. However, the term fatigue may not accurately describe the patient's symptoms[4]. In our experience, patients with SLE often complain of tiredness. This tiredness may reflect profound physical fatigue with reduced energy, irresistible daytime sleepiness, or a mood disorder such as depression. Therefore it is important to determine whether disturbances in sleep/wake physiology and depression contribute to the complaint of tiredness in SLE.

There is some evidence that disordered sleep, sleepiness, and depression may overlap in SLE patients to cause tiredness. Patients with SLE report poor sleep quality, frequent awakenings, and restlessness[5-9]. A recent study of a small group of 14 outpatients with SLE described a high frequency of primary sleep disorders[5]. Mild to moderate sleep apnea with a frequency of 10 or more hypopneas/apneas per hour of sleep were reported in 3 of the 14 patients, and a further 4 had slight disturbances in breathing during sleep. Abnormal periodic limb movements were seen in 7/14 patients, of whom 5 did not have respiratory problems. The SLE patients were more sleepy than the control group and two-thirds described symptoms of depression. Several other studies have found links between depression and changes in sleep in SLE patients[6,7], including the finding that depressed mood con-

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Supported by grants from the University of Toronto Medical Alumni Association.

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Accepted for publication July 7, 2006.

tributes to poor sleep quality in SLE as measured by a standardized sleep quality questionnaire[9]. Disturbances in sleep are well known as a core symptom of depression[10], and depression-associated loss of concentration and lethargy can also masquerade as tiredness.

The purpose of our study was two-fold. First, we aimed to clarify the nature of the complaint of fatigue by describing the prevalence of disordered sleep, excessive daytime sleepiness, and depression in a group of SLE patients complaining of overwhelming fatigue. We then divided the patients into 2 groups, sleepy and non-sleepy, and investigated whether their sleepiness was associated with disordered sleep, medications, disease activity, or depressive symptoms.

MATERIALS AND METHODS

Patients. The subjects consisted of a group of patients with SLE whose disease was not acutely active but who complained of overwhelming tiredness, that is, a level of tiredness that interfered with their usual daily activities. They were assessed at the Sleep Disorders Clinic of the Centre for Sleep and Chronobiology between 1998 and 2003 using overnight polysomnography followed by the multiple sleep latency test (MSLT), a standard test of daytime somnolence. All patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE[11]. The patients were followed prospectively at the University of Toronto Lupus Clinic according to a standardized protocol. Assessment of disease activity was by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K)[12], disease damage by Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index[13], and assessment of fibromyalgia by ACR criteria[14]. Of 52 SLE patients who had polysomnography, 39 had both overnight polysomnographic data and daytime assessment with the MSLT. Four patients were not participants in the Lupus Clinic research protocol and were excluded, leaving 35 patients to comprise the cohort for this study. Of the 13 SLE patients who did not undergo the MSLT, 3 had been referred for investigation of insomnia as their primary complaint and one was a shiftworker. No explanation could be found for why the remaining 9 patients did not undergo the MSLT: there was no difference between this group and the final cohort of 35 patients in the measures of fatigue, depression, sleepiness, or overnight polysomnography.

Thirty-one of the 35 patients were women, 40% were employed, 28% were disabled, 22% were homemakers, and 9% were students. They ranged in age from 23 to 66 years (mean 44 ± 11). Two patients lived with children under the age of 5 years. The mean duration of disease was 127 ± 80 months. The majority (70%) met the ACR criteria for fibromyalgia. Most patients were taking multiple medications (Table 4). Nineteen of the 35 took corticosteroids, 19 took antimalarials, 3 used regular benzodiazepines, and 6 were taking an antidepressant.

Controls. First-night polysomnography studies from 17 healthy, asymptomatic volunteers were used as controls. Nine of the 17 controls were women, and the average age was 28 ± 6.2 years (range 21–41).

Sleep assessment. Overnight polysomnography comprised a standard protocol including electroencephalogram (EEG, C3-A2, C4-A1, Oz), electro-oculogram (EOG), electrocardiogram, submental electromyogram (EMG), right and left anterior tibialis EMG, uncalibrated plethysmographic thoracic and abdominal bands, oro-nasal thermistor, and finger pulse oximetry. All polysomnograms were manually scored blindly according to standard criteria[15]. Arousals were scored based on the Rechtschaffen and Kales definition[15]. In addition, alpha EEG frequencies in non-rapid eye movement (REM) sleep (7.5–11.5 Hz) were scored blindly on a scale from 1 to 5 using a global rating (1 = 0–20%, 2 = 20–40%, 3 = 40–60%, 4 = 60–80%, and 5 = 80–100% alpha frequencies in stages 2, 3, 4 of sleep) according to Maclean, *et al*[16]. The MSLT was performed during the day after the overnight study and consisted of a series of 4 consecutive 20 min nap opportunities at 2 h intervals starting at 9:00 AM[17].

Sleepiness was rated subjectively with the Epworth Sleepiness Scale (ESS)[18] and objectively with the MSLT. Those patients with a mean MSLT sleep onset latency of less than 10 min on 4 nap opportunities were categorized as sleepy[19]. Nap opportunities in which no sleep occurred were included in the average and counted as 20 min. Depression was self-rated using the Beck Depression Inventory (BDI)[20]. Of the 35 patients in this study, 27 had completed the BDI and 29 had completed the ESS at the time of their overnight study. Statistical analysis was performed using the 2-tailed Student t test or chi-square test as appropriate.

HLA typing. One patient diagnosed with narcolepsy was HLA Class II-typed by an experienced technician using the Dynal RELI SSO HLA typing kit.

RESULTS

Sleep. See Table 1 for a summary of selected sleep variables. Compared to healthy controls, SLE patients' sleep had poorer sleep continuity as exemplified by low sleep efficiency (total sleep time/time in bed attempting to sleep; $p < 0.02$) and a high number of arousals per hour of sleep ($p < 0.01$). The sleep stage distribution of SLE patients was skewed towards lighter sleep, with increased stage 1 sleep ($p < 0.02$), decreased stage 3/4 slow-wave sleep ($p < 0.02$), and a high percentage of alpha frequency intrusion into non-REM sleep.

All patients had at least one sleep abnormality (Table 2). Over 75% of patients had a significant level of alpha EEG sleep (i.e., score ≥ 3 on a scale of 1 to 5[16]). Using the conservative criterion of > 10 apneas and hypopneas per hour of sleep, 9 patients were diagnosed with obstructive sleep apnea with a mean apnea/hypopnea index (AHI) of 19.3 ± 10 per hour of sleep. Overall, 20/35 patients had some degree of sleep respiratory disturbance (AHI > 5). Eight patients were found to have periodic limb movement (PLM) disorder employing the conservative criterion of more than 10 involuntary leg movements per hour of sleep, with a mean PLM index of 31.1 ± 15. Three patients with PLM index > 10 also met criteria for obstructive sleep apnea. Leg EMG activity > 5 movements per hour of sleep was recorded in 12/35 patients, and was associated with movement arousals (> 5/h) in 8/35 patients. Of the 12 patients with PLM index > 5, 7 also had AHI > 5.

Table 1. Overnight polysomnography: sleep architecture. Values are mean ± standard deviation except where indicated.

	Healthy Controls, n = 17	SLE Patients, n = 35	p*
Total sleep time, min	381 ± 46	377 ± 98	NS
Sleep efficiency, %	85.7 ± 10	75.0 ± 19	< 0.02
Arousals/hour sleep	2.61 ± 1.7	4.26 + 2.6	< 0.01
Stage 1 sleep, %	7.44 ± 4.2	11.3 ± 6.6	< 0.02
Stage 2 sleep, %	54.2 ± 4.6	57.8 ± 8.5	NS
Stage 3/4 sleep, %	16.2 ± 6.0	11.0 ± 8.2	< 0.02
REM sleep, %	20.9 ± 5.1	19.2 ± 8.6	NS
REM onset latency, min	88.1 ± 36	92.3 ± 60	NS
Alpha-EEG score ≥ 3, no. of patients	4	27	< 0.001

* Controls vs SLE. NS: not significant.

Table 2. Overnight polysomnography: sleepy vs non-sleepy.

	Sleepy, n = 18	Non-sleepy, n = 17	p*
Sleep architecture			
Total sleep time, min	386 ± 98	367 ± 96	NS
Sleep efficiency, %	76.5 ± 19	73.0 ± 19	NS
Arousals/hour sleep	3.77 ± 1.9	4.78 ± 3.1	NS
Stage 1 sleep, %	11.1 ± 5.9	11.5 ± 7.3	NS
Stage 2 sleep, %	58.5 ± 9.3	57.0 ± 7.2	NS
Stage 3/4 sleep, %	11.4 ± 7.6	10.7 ± 8.8	NS
REM sleep, %	18.0 ± 8.6	20.5 ± 8.4	NS
REM onset latency min	105 ± 73	79.0 ± 37	NS
Sleep pathology, no. of patients			
Alpha-EEG score ≥ 3	14	13	NS
AHI > 5	10	10	NS
AHI > 10	4	5	NS
Total PLM > 5/h	2	10	< 0.004
Total PLM > 10/h	2	6	NS
PLM + arousal > 5/h	2	6	NS
PLM + arousal > 10/h	2	3	NS
Narcolepsy	1	0	NS

* Sleepy vs non-sleepy. AHI: apnea/hypopnea index (no. of apneas/hypopneas per h of sleep). PLM: periodic leg movements.

One 36-year-old patient fulfilled standard sleep and clinical criteria for narcolepsy/cataplexy, describing episodes of collapse (being unable to move or speak) precipitated by laughter or anger and occurring since her teens. She was negative for the DR2 and DQB1*0602 HLA alleles that are commonly associated with idiopathic narcolepsy[21].

Sleepiness and depression in SLE. As a group, the average MSLT sleep latency was 10.3 ± 5.0 min (Table 3). Only one patient did not sleep during any naps, while 60% achieved sleep in all 4 naps (data not shown). Based on the mean MSLT sleep onset latency, the SLE patients were divided into 2 populations: sleepy patients with mean onset to EEG sleep less than 10 min (n = 18; mean 6.3 ± 2.0 min), and non-sleepy patients with a mean greater than 10 min (n = 17; mean 14.4 ± 3.5 min). Most of these objectively sleepy patients did not describe an abnormal propensity for sleep as measured subjectively by the ESS, with only 4/16 having scores > 10 out of a maximum score of 24[18]. However, on average, the sleepy group did report a significantly greater susceptibility to falling asleep than the non-sleepy group (ESS mean scores of 6.8 ± 4.9 vs 2.8 ± 3.2, respectively; $p < 0.02$).

Altogether, the study group reported mild to moderate depression on the BDI (mean BDI = 15.8 ± 9.9). The non-sleepy patients rated themselves as significantly more depressed than sleepy patients (20.6 ± 10 vs 11.4 ± 7.1; $p < 0.02$). More non-sleepy patients were moderately depressed (BDI > 17, 17% vs 47%; $p < 0.04$). Two questions on the BDI refer to sleep and fatigue symptoms. To confirm that these questions did not account for the differences between the 2 groups, we repeated the comparison with those questions excluded, and the difference remained statistically significant (8.8 ± 6.0 vs 17.2 ± 9.7; $p < 0.02$). To address the concern that the BDI is overly weighted towards physical symptoms[22], the analysis was repeated, dividing the inventory into cognitive and somatic domains[23]. The non-sleepy patients had significantly greater BDI scores in somatic domains, but not the cognitive domain. There was no difference between the 2 groups in the use of antidepressant medication. Of the 8 patients who were not sleepy and who reported moderate to severe depressive symptoms, only 2 were using antidepressant medications.

The sleep pathology and sleep architecture from the previous night's sleep did not differ significantly between the sleepy and non-sleepy patients, with the exception of PLM (Table 2). A greater number of non-sleepy patients had a notable amount (> 5/h) of leg movements during sleep (10 vs 2; $p < 0.04$). The sleepiness of the SLE patients could not be accounted for by any one medication (Table 4). No association was found between sleepiness and disease activity at the time of the study: comparing sleepy and non-sleepy, the SLEDAI-2K score (2.71 ± 2.64 vs 4.71 ± 4.06) and the SLICC score (1.65 ± 1.66 vs 1.56 ± 2.03) were not significantly different. A similar proportion of sleepy and non-sleepy patients had been diagnosed with fibromyalgia (71% vs 69%) or had a previous history of neuropsychiatric SLE (17% vs 12%).

DISCUSSION

The lupus literature homogenizes tiredness related to sleepiness, depression, and physical exhaustion into one word, fatigue. The results of our study illustrate that many in this

Table 3. Sleepiness and depression. Values are mean ± SD unless otherwise indicated.

	Total, n = 35	Sleepy*, n = 18	Non-Sleepy, n = 17	p
Sleep latency, min	10.3 ± 5.0	6.32 ± 2.0	14.4 ± 3.5	< 0.001
ESS		6.8 ± 4.9 (n = 16)	2.8 ± 3.2 (n = 13)	< 0.02
BDI		11.4 ± 7.1 (n = 14)	20.6 ± 10.4 (n = 13)	< 0.02
CD BDI		5.0 ± 4.5	9.8 ± 7.7	NS (p = 0.06)
SD BDI		6.5 ± 3.3	10.0 ± 4.1	< 0.03
BDI > 17, no. of patients		3	8	< 0.04

* Mean daytime sleep latency < 10 min. ESS: Epworth Sleepiness Scale score. BDI: Beck Depression Inventory score. CD: cognitive domain. SD: somatic domain.

Table 4. Medications taken by the patients with SLE.

Medication	No. of SLE Patients (%) Sleepy	Non-Sleepy	p
Corticosteroids	11 (61)	8 (47)	NS
Antimalarials	9 (50)	10 (59)	NS
Immunosuppressives	4 (22)	4 (24)	NS
Benzodiazepines	2 (11)	1 (6)	NS
Antihypertensives	4 (22)	2 (12)	NS
Antidepressants	3 (17)	3 (18)	NS
Anticoagulation therapy	2 (11)	0	NS
Thyroid hormone	1 (6)	2 (12)	NS
Ca+ channel blocker	3 (17)	4 (24)	NS
NSAID	4 (22)	5 (29)	NS
Estrogen hormone therapy	4 (22)	1 (6)	NS
Gastric acid pump inhibitors	6 (33)	5 (29)	NS

group of typically "fatigued" SLE patients experience poor sleep and are sleepy or depressed.

We found that the sleep of tired SLE patients, compared to healthy controls, was characterized by low sleep efficiency, deficits in slow-wave sleep, frequent awakenings, and high levels of alpha EEG sleep activity. This pattern of sleep is consistent with the pattern of unrestorative sleep described in patients with fibromyalgia[24]. Each patient had at least one identifiable sleep disorder, including 77% with a high level of alpha-EEG sleep, 26% with sleep apnea, and 23% with PLM.

An important limitation of our study is the presence of a first-night effect[25], which may account for some of the sleep changes seen in the SLE patients, including the long REM latency and decreased REM sleep. We have attempted to control for this effect by using unhabituated healthy volunteers as a comparison group. Future studies will replicate these sleep studies over several nights to establish whether these sleep changes are variable or constant, and will include non-tired SLE controls. A possible source of bias in our study is the exclusion of 9/52 SLE patients who did not undergo an MSLT study following their overnight polysomnography. We could not find any systematic reason for this oversight or any difference between this group and the study group, and we thus believe that any potential bias is negligible.

The results of our study are consistent with previous research describing a high prevalence of sleep disorders in patients with SLE[5]. Our group of SLE patients differs from the group studied by Valencia-Flores, *et al*[5] in 2 respects: our group described a disabling level of tiredness and most have been diagnosed with coexistent fibromyalgia. About 11–22% of SLE patients are reported to have comorbid fibromyalgia[26,27], whereas two-thirds (70%) of our study group were diagnosed with this additional disorder. Depression, fatigue, and self-reported disturbed sleep have all been associated with the diagnosis of fibromyalgia in SLE[28].

Most notably, over half of the tired SLE patients in our study were excessively sleepy by objective measures. The role of excessive daytime sleepiness in SLE has not been previously explored, although it contributes to tiredness in chronic fatigue syndrome[29] and in adult and juvenile rheumatoid arthritis[30-33]. Most of the SLE patients underestimated their sleepiness on the ESS. The underreporting of sleepiness by patients is a common phenomenon: sleepy patients with obstructive sleep apnea prefer to describe their condition as fatigue, lack of energy, or tiredness rather than as sleepiness[34].

Several studies have proposed models whereby depression and sleep problems mediate changes in the level of fatigue in SLE patients[6,7]. Our study expands on these models: many of our group of SLE patients with disabling tiredness were found to have poor quality sleep and many were depressed. However, we found that sleepiness in SLE patients was not associated with depression. Rather, those SLE patients with the worst depressive symptoms complained of tiredness, but were not objectively sleepy. Daytime alertness in depressed patients, despite sleep restriction and subjective feelings of tiredness, has been reported[35], but has not been explained. One possibility is that this hyperarousal is secondary to neuroendocrine changes related to depression or chronic pain.

We found no difference between the sleepy and non-sleepy SLE patients in any specific sleep variable or in the prevalence of most sleep disorders. This finding is unexpected, as daytime sleepiness is often related to poor quality or insufficient quantity of sleep. Two explanations are possible: the non-sleepy patients are resistant to somnolence despite a disturbed nighttime sleep, or the sleepy patients are sleepy for a reason other than sleep deprivation. Of interest, the non-sleepy patients had more PLM than sleepy patients. This is consistent with a previous study that found that patients with PLM who complain of persistent difficulties in initiating or maintaining sleep had more fragmented nighttime sleep than those with the complaint of excessive daytime sleepiness[36]. Lupus disease activity measures or the presence of neuropsychiatric SLE were also not found to be associated with sleepiness, in keeping with a recent study in which pain severity and disease activity were not found to be significantly related to self-reported sleep disturbance[9]. The cause of this high prevalence of daytime sleepiness is thus unclear. Although several studies have emphasized that the strongest associations to tiredness in SLE are psychosocial and not inflammatory[1–3,27,37,38], it is still too early to exclude immunological or disease factors. One possibility is that sleepiness is an early symptom of an SLE-related organic brain syndrome. In this study, one of the SLE patients was found to have narcolepsy, the third such case reported[39,40]. A correlation between central nervous system lupus and sleepiness would be interesting in the context of recent research into the hypocretin/orexin neuropeptide[41]. Deficiency in hypocretin/orexin is strongly linked to pathological sleepiness and narcolepsy, and examining its role in SLE would provide a fascinating direction for future research.

In conclusion, we have accepted SLE patients' description of their symptoms as tiredness rather than the more limiting

and ill-defined term fatigue. We have also clarified that tiredness has at least 2 components, sleepiness and depression, and likely a third component that is synonymous with fatigue, physical exhaustion. Investigation of the underlying cause of tiredness in patients with SLE is important for making treatment decisions. However, further research is needed into the effectiveness of different treatment modalities for tiredness in SLE including the use of antidepressants and alerting drugs.

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