Sleep disturbances in patients with systemic lupus erythematosus: A questionnaire-based study

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Abstract

Objective

To assess the prevalence of subjective sleeping complaints by patients with systemic lupus erythematosus (SLE) and to evaluate the correlation between various sleeping complaints and disease activity.

Methods

A standardised sleep questionnaire, The Uppsala Sleep Inventory, was used to investigate the sleeping habits of 30 out-patients with systemic lupus erythematosus (SLE) in comparison to population-based age- and sex-matched controls.

Results

Sleep deficit (difference between need of sleep and actual sleeping time) was similar in patients with SLE (0.8 ± 0.9 hour) and age-matched female controls (0.4 ± 0.8 hour). However, patients with SLE reported more frequent disturbances due to pain, both when trying to fall asleep ($p < 0.01$) and during the night ($p < 0.01$). They also reported frequent awakenings due to headache ($p < 0.01$) and disturbances due to other vegetative symptoms. Furthermore, the SLE patients were awake for significantly longer periods during the night and they estimated their degree of fatigue as significantly higher than the female controls ($p < 0.0001$).

Conclusion

Patients with SLE seem to get a fairly normal amount of sleep, but are frequently disturbed by pain and by various vegetative symptoms, e.g. breathlessness, sweating, and palpitation, which indicate not only pain but also possible involvement of the nervous system. The nervous system may therefore play a role in sleep disturbances reported by patients with SLE.

Key words

Systemic lupus erythematosus, sleep disturbance, sleep questionnaire.

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Introduction

Sleep is a basic biological process possibly related to restorative activity (1). Clinically, poor sleep is a common complaint in various types of illnesses, especially in pain disorders. Sleep disturbances in rheumatoid arthritis (RA), ankylosing spondylitis, osteoarthritis and in "fibrositis syndrome" are well documented (2-7). The explanations for these sleep disturbances include joint pain, stiffness and muscular discomfort. We have also reported significant sleep disturbances in patients with primary Sjögren's syndrome (8), and it has been reported that women with SLE also experienced a high frequency of sleep disturbance (61%) before attending an aerobic conditioning program (9). McKinley and co-workers reported that female SLE patients tended to report more problems with sleep than healthy control women and they postulated that sleep and depression contributed to the fatigue frequently associated with SLE (10). In connection with this, Tench *et al.* also reported an association between fatigue and disease activity, sleep quality, anxiety and depression in a group of out-patients with SLE (11). Furthermore, recent evidence has pointed out a possible role for the cytokines in the regulation of sleep (12-14), which provides further reason for exploring sleep patterns in patients with inflammatory systemic disorders, e.g. systemic lupus erythematosus (SLE).

A standardized questionnaire was therefore used to examine the prevalence and the pattern of sleep disturbances in a group of outpatients with SLE. The study demonstrated that female patients with SLE are frequently disturbed by pain, but also by breathlessness, palpitation, sweating and headache during the night, or so-called vegetative symptoms. This may indicate that patients with SLE are suffering not only from pain problems, but also that the nervous system may be under the influence of inflammatory cytokines, which may also play a central pathogenic role in sleep disturbances reported by these patients.

Materials and methods

Thirty female outpatients with SLE who arrived one after the other at the Department of Rheumatology, Uppsala University Hospital, Sweden, were included in the study during a 3-month period in the spring. All patients were assessed according to the 1982 criteria of The American College of Rheumatology (15). They had a mean age of 43 ± 14 years (range 21 - 80). The onset of disease had occurred 2 to 31 years (mean 12 years) before the study.

Twenty-four patients were on prednisolone and 11 of these patients were also being treated with azathioprine and one with cyclophosphamide. The glucocorticosteroids were always administered early in the morning, except in those cases where the patients were on a dose higher than 15 mg of prednisolone, when the corticosteroids were given twice daily, in the morning and at lunch time. In addition, 6 patients were on chloroquinum treatment.

Thirty age-matched females taken randomly from a data base of 2000 participants in an earlier population-based study (The Uppsala Sleep Inventory Study) served as controls (16).

The disease activity level was evaluated with the modified Systemic Lupus Erythematosus Disease Activity Index MEX-SLEDAI (17), and by the following laboratory measurements: haemoglobin (Hb; normal 113 - 139 g/l), white blood cells (WBC; normal 4 - 9 10^9/l) and platelet count (normal 150 - 400 10^9/l), erythrocyte sedimentation rate (ESR; normal < 15 mm/hour), S-haptoglobin (normal 0.2 - 1.4 g/l), and C-reactive protein (CRP; normal <10 mg/ml). All patient sera were also analysed for the existence of ANA, anti-DNA, SSA and SSB, respectively.

Sleep questionnaire

All patients received a sleep questionnaire by mail: The Uppsala Sleep Inventory, which has been used in several epidemiological studies (16, 18-20). The questionnaire consists of 87 questions, of which 37 are statements about the degree or the frequency of sleep complaints on a five point-scale from "no problems", "rarely", "sometimes", "often or great" to "very often or very

Table I. Disease activity in 30 female patients with SLE measured by the MEX-SLEDAI. This disease activity index described the symptoms present at the time of the visit for the study or in the 10 days preceding the visit.

Case no.	Age in years	Disease duration	Neurological disorders (8 points)	Renal disorder (6 points)	Vasculitis (4 points)	Hematological disorders (3 points)	Myositis (3 points)	Arthritis (3 points)	Mucocutaneous disorder (3 points)	Serositis (2 points)	Fever fatigue (1 point)	Lympho- or leukopenia (1 point)	Total score
1	25	11	-	proteinuria	-	-	-	-	malar rash	-	fatigue	leukopenia	10
2	38	16	-	-	-	-	-	-	malar rash	-	fever	-	3
3	45	14	mononeuritis	-	-	hemolysis	-	-	alopecia	-	fatigue	-	14
4	31	5	-	-	-	-	-	-	mucocut.dis	-	fever	-	3
5	56	16	org brain syndr	-	-	-	-	-	malar rash	-	fatigue	-	11
6	40	7	-	-	-	-	-	-	mucocut.dis	-	-	leukopenia	3
7	68	9	-	-	-	-	-	-	-	-	fatigue	lymphopenia	2
8	35	14	mononeuritis	-	-	-	-	-	-	-	fatigue	leukopenia	10
9	42	4	-	-	-	-	-	-	malar rash	-	-	lymphopenia	3
10	21	8	org brain syndr	casts	-	-	-	-	alopecia	-	-	-	16
11	53	13	-	hematuria	-	-	-	-	-	-	fatigue	-	7
12	58	4	-	-	-	-	-	-	-	-	fatigue	-	1
13	55	16	-	-	-	-	-	-	-	-	-	-	0
14	23	4	-	-	-	-	-	arthritis	mucocut.dis	-	fever	-	5
15	80	6	mononeuritis	-	-	-	-	-	-	-	-	-	8
16	46	19	-	-	-	-	-	-	mucocut.dis		fatigue	-	3
17	36	15	-	-	-	-	-	-	mucocut.dis	-	fatigue	-	3
18	46	28	-	-	-	-	-	-	-	-	-	-	0
19	32	12	-	nephritis	-	-	-	-	mucous ulcer	-	fever	lymphopenia	10
20	50	30	CVA	-	-	-	-	-	malar rash	-	-	-	10
21	27	3	-	nephritis	-	-	-	-	-	-	-	-	6
22	42	31	-	-	-	-	-	-	-	-	fatigue	-	1
23	72	4	-	-	-	-	-	-	-	-	fatigue	-	1
24	26	2	-	-	vasculitis	-	-	-	malar rash	-	fatigue	-	7
25	40	6	-	-	-	-	-	-	alopecia	-	fatigue	-	3
26	36	6	-	-	-	-	-	-	-	-	-	leukopenia	1
27	47	8	org brain syndr	-	-	-	-	-	mucocut dis	-	fatigue	-	11
28	49	11	-	-	-	-	-	-	-	-	fatigue	-	1
29	50	12	-	-	-	thc penia	-	arthritis	malar rash	-	fever	-	8
30	37	11	-	creat incr	-	-	-	-	-	-	-	-	6

CVA = cerebral vascular accident; creat incr = increase in creatinine; mucocut dis = mucocutaneous disorder; org brain syndr = organic brain syndrome; trc penia = thrombocytopenia.

great problems". The distribution of responses in the last two categories ("great" or "very great"; and "often" or "very often") were used in the analysis. One question used a 10-grade visual analogue scale to investigate the degree of fatigue.

Statistics

The chi-square and Mann-Whitney U tests was used for the comparison of the patients and controls. Relationships between continuous variables were calculated using the Spearman Rank correlation test. After Bonferroni, correction only p-values of < 0.01 or better were considered significant.

Results

Clinical data

According to the MEX-SLEDAI eight patients had a score of > 9, i.e., active disease, while the remaining 21 patients had a score of 8 or less (Table I). The whole group had a mean score of 5.6 ± 4 (range 0 - 16). The means and actual ranges in our patient sample of the following laboratory data were: 22 mm (3 - 70) for ESR; 1.8 g/l (0.5 - 5.6) for S-haptoglobin; 126 g/l (70 - 152) for Hb and 7.0 (3.0 - 20.8) for WBC. Four patients had an elevated CRP (> 10 g/l). One patient had severe anaemia (70 g/l), while five patients had mild anaemia (100 - 113 g/l).

General variables concerning sleep

Fifty percent of the SLE patients and 25% of the female controls considered that they received "too little sleep". However, patients with SLE estimated their hours of sleep and need of sleep as similar to that of the controls (Table II). Furthermore, the calculated sleep deficit, i.e., the mean difference between need of sleep and actual sleeping time, was also two-fold higher in the SLE group, but the difference was not significant (0.8 hrs ± 0.2; 0.4 hrs ± 0.1, respectively).

Sleep disturbances

Patients with SLE had a significantly higher frequency of pain complaints when trying to fall asleep ($p < 0.01$) and during the night ($p < 0.01$) compared with the age-matched controls.

Table II. Self-rated variables concerning sleep and need of sleep in 30 patients with systemic lupus erythematosus (SLE) compared with 30 age-matched female controls. The data are presented as means ± SEM.

	SLE	Controls
- Time in bed before attempting to fall asleep (min)	18 ± 3.0	22 ± 1.6
- Time taken to fall asleep (min)	21 ± 4.6	19 ± 1.3
- Sleeping time, hrs	7.2 ± 0.2	7.2 ± 0.1
- Need of sleep, hrs	7.9 ± 0.2	7.6 ± 0.1

No significance was observed between the SLE patients and controls.

Table III. Self-rated symptoms expressed as percentages of ratings of the two highest scores on a 5-point scale in 30 patients with systemic lupus erythematosus (SLE) and in 30 age case-control matched females.

	SLE	Controls
Symptoms when trying to fall asleep		
- difficulties falling asleep	9.7	16.1
- pain	41.4*	9.7
- muscular tension	30.0	16.1
- restless legs	10.0	10.0
- racing thoughts	22.6	13.0
Symptoms during the night		
- awakenings during the night	9.7	22.6
- awake > 30 minutes during the night	23.3*	0.0
- pain during night	26.7*	0.0
- waking up with headache	32.3*	3.2
- sweating	13.3	0.0
- loud snoring	3.3	3.3
- palpitations	3.3	0.0

Significance (p value): SLE vs. controls: * = $p < 0.01$.

The questionnaire does not differentiate between arthralgia and myalgia, but only contains question about general pain.

The SLE group also reported higher frequencies, though not significantly higher, of problems due to muscular tension and racing thoughts when trying to fall asleep. However, the SLE patients did not report problems with initial insomnia; on the contrary, the age-matched females in the control group reported a higher frequency of difficulties when falling asleep, 16% vs. 9.7%, respectively (Table III). A frequent use of hypnotics was reported by 6% of the SLE patients but by none of the female controls. Disturbances related to environmental factors such as noise, light and temperature were similar in both groups (data not shown).

The SLE patients did not report a higher number of nocturnal awakenings, but when wakened they were awake for longer periods (>30 min) during the night compared with the control group ($p<0.01$); this was most frequently due to nocturnal pain ($p < 0.01$), headache ($p < 0.01$) and sweating (Table III).

Daytime symptoms

Patients with SLE reported significantly more frequently that they suffered from fatigue during the day ($p < 0.001$), and that they also took naps more frequently ($p < 0.01$) than the age-matched females. The SLE patients reported also that they did not feel “rested by sleep” more frequently than the controls, but this difference did not reach statistical significance (Table IV).

The SLE patients estimated their global degree of fatigue on a 10-grade visual analogue scale as 5.6 ± 0.6, in comparison to 2.8 ± 1.3 ($p<0.0001$) by the controls. Fifty-four percent of the SLE patients believed that their sleeping habits disturbed their daily activities,

Table IV. Self-rated daytime symptoms expressed as percentages of ratings of the two highest scores on a 5-point scale in 30 patients with systemic lupus erythematosus (SLE) and in 30 age case-control matched females.

	SLE	Controls
Symptoms during the day		
- fatigue during day	45.2**	6.7
- nap during day	30.0*	0.0
- not rested after sleep	34.5	16.7
- daytime sleepiness	30.0	25.8

Significance (p value): SLE vs. controls: * $p < 0.01$; ** $p < 0.001$.

while only 10% of the controls reported the same feeling.

Disease activity and sleeping complaints

The nine patients with a high score on the MEX-SLEDAI reported with a significantly higher frequency disturbances during the night due to palpitations ($p < 0.01$), shortness of breath ($p < 0.01$) and periods of paralysis; furthermore, they also reported more frequently that they were not rested after sleep ($p < 0.01$). Patients with central nervous system (CNS) involvement also reported significantly more frequently disturbances during the night due to vegetative symptoms, i.e., palpitations ($p< 0.01$), shortness of breath ($p < 0.01$) and headache ($p < 0.01$).

No correlation was found between measured laboratory parameters or serological markers and no significant differences were observed regarding sleep complaints in relation to whether or not patients were treated with corticosteroids or disease-modifying antirheumatic drugs.

Discussion

The present study indicates that patients with systemic lupus erythematosus suffered from significant difficulties in maintaining sleep, mainly due to nocturnal pain, leading to long periods of sleeplessness during the night. Furthermore, the SLE patients also reported significant disturbances due to vegetative symptoms stemming from the autonomic nervous system, e.g., breathlessness, sweating, palpitation and headache. These vegetative symptoms correlated with the disease activity evaluated by MEX-SLEADI, especially in those patients with clinical involvement of the CNS.

Although the SLE patients were disturbed a significant number of times by general pain problems when falling asleep, they did not report initial insomnia, nor did they report more frequent awakenings during the night than did the age-matched controls. However, when the SLE patients were wakened they were awake for longer periods during the night, mostly because of pain and headache and other vegetative symptoms. Thus, patients with SLE seem to have frequent difficulties due to pain and symptoms from the autonomic nervous system, indicating that the involvement of the CNS may play a role in the pathogenesis of sleep disturbances reported by patients with SLE.

Our results are partly in contrast to the results reported by McKinley and coworkers (10). They reported that their SLE patients tended to have longer sleep latencies and that their patients got more sleep per night than their controls, whereas our patients were similar in that respect to our population-based controls, but had significantly more disturbances during the night due to pain and vegetative symptoms. McKinley used a 12 item questionnaire, which had not been standardized, while we used a well-standardized questionnaire of 87 items which has previously been used in several epidemiological studies (16, 18-20). Tench and co-workers (11), who reported that 60% of their patients with SLE had poor sleep quality, used the Pittsburgh Sleep Quality Index, a self-rated questionnaire comprising 19 different items that generate an overall sleep-quality score. On the other hand, The Uppsala Sleep Inventory affords the possibility of analysing the prevalence of different complaints, both when the patient is trying to fall asleep as well as during the night, and of comparing these complaints with different clinical parameters.

Several studies have also reported an increased frequency of sleep disturbances in patients with various rheumatic disorders, i.e., rheumatoid arthritis (2,7),ankylosing spondylitis (6), osteoarthritis (4) and fibromyalgia (21). We have also recently reported frequent sleep disturbances in patients with primary Sjögren's syndrome (8). Most studies claim pain as the major underlying factor as regards the sleep problems experienced by patients with rheumatic diseases, a finding which is confirmed in this study. Leigh *et al.* (4) did not find any differences in the level of sleep disturbances between rheumatic and non-rheumatic hospitalised patients, except that pain was more frequently cited by the rheumatic patients. Since pain is a major problem in arthritic patients and in our patients with SLE, it is worth noting that Lavie *et al.* found that non-steroid anti-inflammatory drugs improved the RA patients' clinical condition as regards nocturnal pain, as it does for morning stiffness, but failed to observe any improvement in objective sleep parameters (22).

The present study demonstrates that it is important to analyse sleep complaints in patients with rheumatic diseases when they contact doctors because of insomnia or daytime fatigue, since sleep disturbances may be primarily a pain problem. In this way, analgesics and/or non-steroid anti-inflammatory drugs could be the first drugs of choice rather than hypnotic drugs in these cases. However, non-steroid anti-inflammatory drugs may give rise to some cerebral-related symptoms, and thus further complicate the daytime symptoms reported by patients with SLE. However, a more complicated pathogenesis, i.e., involvement of the nervous system due to the systemic effects of inflammatory cytokines, may also play a role in the sleep disturbances reported by patients with SLE. In the present study, sleep complaints

were more frequently reported by patients with more active disease symptoms as evaluated with the MEX-SLEDAI, especially those with involvement of the CNS, than those with less active disease symptoms.

Patients with SLE and other systemic rheumatoid disorders are frequently treated with corticosteroids and other immunosuppresants. Glucocorticosteroids, at least in high doses, may give rise to sleep problems and some psychiatric symptoms. However, we did not find any differences in the sleep complaints of SLE patients on corticosteroids and those who were not, nor did Mahowald and co-workers in patients with rheumatoid arthritis (23). Furthermore, Valencia-Flores and co-workers, who evaluated 14 SLE patients in a recent study using all-night polysomnography, did not find any differences in the polysomnographic data on those patients who were on corticosteroids and those who were not being treated with corticosteroids (24). Thus, in the present group low doses of corticosteroids in patients with inflammatory systemic disorders seemed not to have a negative effect on their sleep patterns.

We have recently reported that patients with primary Sjögren's syndrome suffer significantly from difficulties in both initiating and maintaining sleep and that they complain of vegetative and possible neuropsychiatric symptoms when trying to fall asleep (8). These findings are quite similar to the present findings for SLE patients, indicating that the etiology of the sleep disturbances in these two patient groups may be identical. Furthermore, Valencia-Flores and co-workers (24) found that SLE patients had problems due to respiratory and movement disorders, but also a decrease in sleeping efficiency, and that their patients had a delta sleep pattern in their polysomnographic records and sleep fragmentation. Their findings are similar to the polysomnographic findings for patients with primary Sjögren's syndrome (8).

Patients with fibromyalgia or "fibrositis syndrome", like patients with SLE, complain of muscular pain and stiffness (25). However, our SLE patients did not have the tender points necessary to meet the criteria for "fibrositis syndrome". Moldofsky *et al.* found that patients with fibromyalgia (21), as well as RA patients during an acute flare of the disease (7), displayed an anomalous presence of alpha rhythms during non-rapid-eye-movement sleep, as measured by EEGs. Similar findings have been reported in patients with chronic pain for which no physical cause could be found (26) and similar findings have been reported in Sjögren's syndrome (8) and SLE (24). Further studies, with all-night polysomnographic recordings and MRT studies as well as measurements of various cytokines in the spinal fluid and peripheral blood, are needed to better characterise the sleep pattern of patients with SLE and thus elucidate whether or not CNS involvement may be a central etiological factor in the sleep disturbances seen in these patients.

References

1. ADAMS K: Sleep as a restorative process and a theory to explain why. *Progress in Brain Research* 1980; 53: 289-306.
2. HIRSCH M,CARLANDER B, VERGE M, TAFTI M, ANAYA JM, BILLIARD M, SANY J: Objective and subjective sleep disturbances in patients with rheumatoid arthritis: A reappraisal. *Arthritis Rheum* 1994; 37: 41-9.
3. BAYLAY T, HASLOCK I: Night medication in rheumatoid arthritis. *J R Coll Gen Pract* 1976; 26: 591-4.
4. LEIGH T, BIRD H,HINDMARCH I,WRIGHT V: A comparison of sleep in rheumatic and non-rheumatic paitents. *Clin Exp Rheumatol* 1987; 5: 363-5.
5. HART F, TAYLOR R, HUSKISSON E: Pain at night. *Lancet* 1970; 25 (i): 881-4.
6. HULTGREN S, BROMAN JE, GUDBJÖRNSSON B, HETTA J, LINDQVIST U: Sleep disturbances in outpatients with ankylosing spondylitis - a questionnaire study with gender implications. *Scand J Rheumatol* 2000; 29: 365-9.
7. MOLDOFSKY H, LUE F, SMYTHE H: Alpha EEG sleep and morning symptoms in rheumatoid arthritis. *J Rheumatol* 1983; 92: 212-6.
8. GUDBJÖRNSSON B, BROMAN JE, HETTA J, HÄLLGREN R: Sleep disturbances in patients with primary Sjögren's syndrome. *Br J Rheumatol* 1993; 32: 1072-6.
9. ROBB-NICHOLSON LC, DALTROY L, EATON H *et al.*: Effects of aerobic conditioning in lupus fatigue:A pilot study. *Br J Rheumatol* 1989; 28: 500-5.
10. MCKINLEY PS, OUELLETTE SC,WINKELGH: The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus: A proposed model. *Arthritis Rheum* 1995; 38: 826-34.
11. TENCH CM, MCCURDIE I,WHITE PD, D'CRUZ DP: The prevalence and associations of fatigue in systemic lupus erythematosus. *Rheumatol* 2000; 39: 1249-54.
12. OBAL F, OPP M,CADY AB *et al.*: Interleukin 1 alpha and an interleukin 1 beta fragment are somnogenic. *Am J Physiol Regul Integr Comp Physiol* 1990; 259: 439-46.
13. MOLDOFSKY H,LUE FA,EISEN J, KEYSTONE E, GORCZYNSKI RM: The relationship of interleukin-1 and immune functions to sleep in humans. *Psychosom Med* 1986; 48:309-18.
14. REICHLIN S: Neuroendocrine-immune interactions. *N Engl J Med* 1993; 21: 1246-53.
15. TAN EM, COHEN AS, FRIES JF: The 1982 revised criteria for the clessification of systemic lupus erythematosis: *Arthritis Rheum* 1982; 25: 1271-7.
16. HETTA J, ALMQVIST M, ÅGREN H, HAMBERT G, LILJENBERG B, ROOS BE: Prevalence of sleep disturbances and related symptoms in a middle-aged Swedish population. *In:* KOELLAWP and RUTHER E (Eds.): *Sleep 84.* Stuttgart, Gustav Fischer Verlag 1985: 373-6.
17. GUZMÁN J, CARDIEL MH,ARCE-SALINAS A, SÁNCHEZ-GUERRERO J, ALARCÓN-SEGOVIA D: Measurement of disease activity in systemic lupus erythematosus: Prospective validation of 3 clinical indices. *J Rheumatol* 1992; 19: 1551-8.
18. GISLASON T, ALMQVIST M: Somatic diseases and sleep complaints. *Acta Med Scand (J Int Med)* 1987; 221: 475-81.
19. LILJENBERG B, ALMQVIST M, HETTA J, ROOS BE, ÅGREN H: Affective disturbance and insomnia:A population study. *Eur J Psychiatry* 1989; 2: 16-21.
20. LILJENBERG B, ALMQVIST M, HETTA J, ROOS BE, ÅGREN H: The prevalence of insomnia: The importance of operationally defined criteria. *Ann Clin Res* 1988; 20:393-8.
21. MOLDOFSKY H, SCARISBRICK P, ENGLAND R, SMYTHE H: Musculoskeletal symptoms and non-REM sleep disturbance in patients with "Fibrositis Syndrome" and healthy subjects. *Pyschosm Med* 1975; 37: 341-7.
22. LAVIE P, NAHIR M, LORBER M, SCHARF Y: Nonsteroidal anti-inflammatory drug therapy in rheumatoid arthritis patients:Lack of association between clinical improvment and effects on sleep. *Arthritis Rheum* 1991; 34: 655-9.
23. MAHOWALD MW, MAHOWALD ML, BRUNDLIE SR,YTTERBERG SR: Sleep fragmentation in rheumatoid arthritis. *Arthritis Rheum* 1989; 32: 974-83.
24. VALENCIA-FLORES M, RESENDIZ M, CASTANO VA, *et al.*: Objective and subjective sleep disturbances in patients with systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 2189-93.
25. LINDAL E,THORLACIUS S, STEFANSSON JG, STEINSSON K: Pain and pain problems among subjects with systemic lupus erythematosus in Iceland. *Scand J Rheumatol* 1993; 22: 10-3.
26. WITTIG R, ZORICK EJ, BLUMER D, HEILBRONN M, ROTH T: Disturbed sleep in patients complaining of chronic pain. *J Nerv Ment Dis* 1982; 170: 429-31.