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SLEEP IN RHEUMATOID ARTHRITIS: A COMPARISON WITH HEALTHY SUBJECTS AND STUDIES OF SLEEP/WAKE INTERACTIONS

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SUMMARY

Sleep complaints are frequent in patients with rheumatoid arthritis (RA) and sleep disturbances may contribute to pain and other daytime complaints. The aims of the current study were to compare ambulatory sleep recordings from consecutively selected patients with RA to those obtained in healthy controls, and to study the relationships between sleep structure and clinical symptoms. Sleep recordings were obtained from 41 out-patients with RA and 19 matched controls. All had clinical examinations and completed different questionnaires. Recordings were scored traditionally and, moreover, the electroencephalography (EEG) was subjected to frequency analysis. For the study of sleep–wake interactions in the patients, a graphical chain model was used. The patients had many sleep-related complaints. An increase in the number of periodic movements of the legs (PML) during sleep was seen in comparison with controls, but otherwise only minor differences were observed in classical sleep stages. Data from frequency analysis showed an increase in alpha (8–12 Hz)-EEG activity in sleep stages non-rapid eye movement (NREM) 2–4 in most sleep cycles. The statistical model demonstrated a complex but independent correlation between morning stiffness, pain and joint tenderness on the one hand, and awakenings, stage NREM2, slow-wave sleep and stage REM on the other, probably reflecting a relationship between sleep patterns and pain in RA. In conclusion, only the increase in PML and alpha-EEG activity distinguished the sleep in RA patients from that of healthy controls. However, the demonstrated interaction between daytime complaints and sleep patterns may increase the understanding and treatment of the disease. In future research, graphical chain models may improve our understanding of complex relationships between multiple variables.

KEY WORDS: Sleep, Rheumatoid arthritis, Pain, Disease activity, Home monitoring, Graphical chain model, Causal probabilistic network.

SLEEP problems are frequent in medical illness [1–4], and an association between sleep and morbidity, as well as mortality, has been demonstrated [5, 6]. Pain especially may be a leading cause of insomnia in medical patients [4, 7], but on the other hand, disturbances in sleep may also alter the pain threshold [8]. Finally, the disease process *per se*, as well as medication, may influence the sleep process [2, 9].

Accordingly, in most studies, sleep disturbances have been reported by more than half of the patients with rheumatoid arthritis (RA) [10–13]. As sleep disorders may contribute to various daytime symptoms such as fatigue, stiffness and pain [9, 12–17], studies of sleep may have the potential to increase our knowledge of the natural history of the disease. Among other findings, polysomnographic (PSG) recordings have documented a high prevalence of sleep fragmentation, alpha-electroencephalographic (EEG) activity and primary sleep disorders in a limited number of patients [9, 13–15, 18–20]. In some of these studies, the subjects selected had either an exacerbation of the disease [13] or complained of very early onset of fatigue [15]. Moreover, a control group was only included in one previous study [9]. Finally, most PSG studies of sleep in RA were based on recordings obtained in the sleep laboratory. Under these circumstances, sleep may not be natural, unless several nights are used for adaptation to the laboratory. Even then, some subjects may have problems with sleeping in non-familiar surroundings [21]. To address these problems, the current study was performed. The aims were 3-fold. Firstly, to compare the classical sleep stages from recordings obtained at home in non-selected out-patients with RA to those from healthy subjects. Secondly, to study sleep microstructure using power spectral analysis and, finally, to address sleep/wake interactions using multivariate statistics based on graphical chain models.

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METHODS

Patients and controls

Forty-two consecutive out-patients referred to the Departments of Rheumatology and Internal Medicine, Aalborg Hospital, from 1993 to 1995 entered the study. All patients fulfilled the American Rheumatism Association criteria for RA [22] and the

study was approved by the local ethics committee. In one subject, the sleep recording failed due to technical problems, and the patient did not wish to re-enter the study. Nineteen age- and sex-matched healthy subjects served as controls.

Assessments

All patients were classified according to their functional status [23]. A clinical examination was performed on the evening before the sleep recordings. The number of swollen and tender joints and the Ritchie Articular Index [24] were calculated. All tender points normally used in the assessment of fibromyalgia were palpated. Evaluation of the duration of morning stiffness and a three-point physical activity scale were also completed, and the erythrocyte sedimentation rate was measured. Mean daytime sleepiness was measured using a 0–100 mm visual analogue scale ranging from 'no sleepiness' to 'worst imaginable sleepiness', and pain intensity was assessed on a 1–5 verbal scale [25]. For sleepiness and pain, the mean of the score on the day the PSG was performed and the score the following day was calculated. Finally, the following questionnaires were completed before the PSG: the modified Stanford Health Assessment Questionnaire (HAQ) with scores ranging from 0 (best possible) to 24 (worst possible) [26], the Danish version of the McGill Pain Questionnaire (MPQ) [25], a nine-item fatigue scale, all items with scores ranging from 1 (worst possible) to 7 (best possible) [27], and the Basic Nordic Sleep Questionnaire (BNSQ) based on 1 (best possible) to 5 (worst possible) verbal scales [28].

Sleep recordings

All subjects had home PSG recordings performed on two consecutive nights. As a minimal 'first night effect' has been demonstrated using the equipment [29], the first night served as a practice run, and only data from the second night were stored for further analysis. The collecting system was designed for direct sampling of all polygraphic data at the bedside and its reliability as well as technical specifications have been documented previously [29]. The montage consisted of two EEG leads (F1–A2, C4–A1), electro-oculography (EOG) (left eye–A2, right eye–A2), submental electromyography (EMG), bilateral anterior tibial EMG and a respiratory belt. All psychotropic drugs were withdrawn 2 weeks before the study [30], but otherwise patients were on their regular medication. Subjects were only allowed to smoke and drink tea or coffee until 6 p.m. the same day. After applying the electrodes, the head box was disconnected from the main amplifier and placed in a belt. The subjects were allowed to move around freely until their usual bedtime, and they were instructed how to start the recordings themselves by pressing a button on the recording system when the light was turned off. They were allowed to get out of bed during the night if necessary and to get up at the usual time. In the morning, the recordings were stopped by pressing another button on the system and subjects removed the electrodes themselves. The maximum recording time was set at 9½ h in case the computer was not stopped by the patient.

All PSG data were scored manually and blindly by the same physician in 30 s epochs according to standard criteria [31]. The Nightingale system (Judex Datasystems A/S, Aalborg, Denmark) was used for display of polygraphic signals. The sleep period was the time from the onset of non-rapid eye movement (NREM) stage 1 until final awakening. Total sleep time was defined as the time spent in stages NREM1–4 + rapid-eye-movement (REM) sleep. Sleep efficiency was defined as total sleep time as a percentage of sleep period, and slow-wave sleep (SWS) was NREM3 and 4 combined. Total time spent in stage wake (Wake) included sleep latency and all epochs scored as Wake until final awakening. Arousals were scored according to Bonnet *et al.* [32]. Apnoeas and hypopnoeas were analysed [33], and leg movements were detected as increased activity in one or both tibial EMG channels with or without simultaneous arousal [34]. Periodic movements of the legs (PML) [35] were scored separately. The number of arousals (Arousal Index), apnoea/hypopnoeas (Apnoea Index), leg movements (Movement Index) and PML (PML Index) per hour were calculated. No attempt was made to score the alpha-EEG visually, as quantification was performed using frequency analysis.

Frequency analysis

The F1–A2 derivation was selected for frequency analysis. This lead has been shown to be the most stable and noise free in home recordings compared to the C4–A1 derivation [29]. Epochs labelled as artefacts, Wake or movement time were discarded from analysis. The EEG was pre-emphasized 20 dB/decade to expand the amplitudes at high frequencies [36], and frequency analysis of the EEG was performed using autoregressive (AR) modelling [37]. The sleep EEG was divided into five frequency bands, delta (0.5–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), sigma (12–14.5 Hz) and beta (14.5–25 Hz), and for every 2 s segment of the EEG the distribution of normalized power was calculated in these five bands [37]. Finally, the mean power for every 30 s epoch was computed and the power for all sleep stages calculated individually. As sleep appears in 4–6 ultradian NREM/REM cycles throughout the night [39], the analysis was also performed for each sleep cycle. To compute the total amount of power in the delta and alpha bands in every sleep cycle, a calculation was performed where the number of epochs as well as the density of power were taken into consideration. Therefore, in each sleep cycle, the mean power in the two bands was multiplied by the number of epochs in each of the stages NREM2–4 individually and finally summarized to give the total power normalized for each cycle [38].

Statistics

Comparison of patients and controls. The variables were described by the mean and S.D. Data from conventional sleep staging in patients and controls were compared using *t*-tests. As mainly sleep stages NREM2–4 are thought to reflect homeostatic processes, the distribution of the EEG power in these stages was calculated using two-way analysis of variance (ANOVA), where power in the individual frequency bands entered as the dependent variable and sleep stage (NREM2–4) and type (patient versus control) entered as factors.

Relationship between clinical variables. The many parameters and preliminary statistical analysis indicated a complex relationship between the individual variables. As no *a priori* knowledge of the relationship between the variables was given, a model with only stochastic relationships was a proper choice. Therefore, a graphical chain model was selected for final analysis and interpretation of data. The graphical chain models [40] have previously been found to be valuable for discovering and describing structures in a complex, stochastic system. A graphical model for discrete variables, i.e. contingency tables, is a log–linear interaction model that can be represented by a simple graph with as many points as there are dimensions in the table. These models can be given an interpretation in terms of conditional independencies which can be read off the graph (in the form of a Markov property). Thus, hypotheses are formulated about relationships of variables, using points for variables and lines for each pair of variables having some relationship. Most importantly, a missing line corresponds to the conditional independence of the two variables in case. The computational method had a multivariate design, where the starting point was a 'full model', i.e. a model with all possible connections between the variables. To identify a minimal and unique model, backward elimination and forward selection were used. Elimination and selection refer to removing or adding a line during an interactive process. Whether a line should be removed (or added) is based on a likelihood ratio test using exact *P* values, where the model including the line is tested against the model without the line. Following the first calculations, a retesting of all variables was performed where the new information obtained was included in the model. This testing was carried out an indefinite number of times until stability of the system was reached. If a significant relationship between variables was reached at a significance level of 0.05, this was indicated by a line. The line thus shows a significant relationship between two variables independent of the multiple relationships between the others, i.e. a change in one parameter is followed by a change in the other [41]. Finally, all variables and the relationships between them were described in a graphical presentation referred to as the 'initial model'.

As data should be represented by a contingency table, they were divided into levels dependent on the actual values if these were discrete. Some values were merged into one level if there were too few data within this level to ensure validity of the likelihood-ratio tests. Continuous variables, however, were divided into three levels using the 33 and 66% percentiles. This reduction was necessary to ensure a reasonable amount of data for each level of a given variable. The following parameters were selected for inclusion in the model: type [RA/N (normal)], sex, duration of disease, HAQ score, morning stiffness, Ritchie and pain scores, erythrocyte sedimentation rate, fatigue and sleepiness scores, physical activity score, sleep quality, percentage time spent in stage Wake, NREM1–4 and REM, number of stage shifts, Arousal and Movement Index, and normalized power in the five frequency bands in stage NREM2–4 merged.

In the next step, a subset of variables was selected. The reason for the reduction was firstly that the initial model was too complex to give any clear interpretation of the data and, secondly, that the amount of data was too small to ensure a unique model, i.e. the number of variables has to match the amount of data. According to the relationships seen in the initial model and a selection of the variables which have previously been focused on in sleep/wake interactions, the procedure included the following 15 variables: type, duration of disease, pain level, Ritchie score, morning stiffness, time spent in stage Wake, NREM2, SWS and REM, number of stage shifts, Arousal Index and power in delta, theta, alpha and sigma bands. The relationships between variables in the refined system were computed using the methods described above. In the presentation of the final model, a causal probabilistic network (CPN) shell was implemented (Hugin Expert A/S, Aalborg, Denmark). Using this shell, routines are available for the calculation and presentation of marginal densities, i.e. the percentage distribution within each level of a given variable [42]. Thus, complex relationships between sleep/wake interactions could finally be simulated and dynamic examples for the use of the system presented.

RESULTS

Clinical and demographic data

Forty-one patients with RA completed the study. These were 11 males and 30 females, mean age 53.2 yr (13.9). None had other medical diseases or disorders known to interfere with sleep. The mean duration of disease was 162 months (114.0) and the mean Steinbrocker Index was 1.6 (0.8). Erythrocyte sedimentation rate was 22.3 (14.3). The number of swollen and tender joints was 9.6 (9.0) and 5.8 (6.1), respectively, and the tender point count was 5 (5.5). Mean Ritchie score was 14.4 (12.3). Morning stiffness was 64.5 min (77.3) and the physical activity score was 1.6 (0.5). Mean fatigue score was 2.7 (1.3) and sleepiness score 48.0 (24.9). Mean daytime pain intensity was 1.8 (1.0) and from the MPQ the Total

TABLE I
Selected variables from the Basic Nordic Sleep Questionnaire in which answers are given on a 1–5 verbal scale where 1 represents no sleep disturbances and 5 means severe sleep problems. Data are presented as the mean (S.D.)

	Rheumatoid arthritis	Controls
Difficulties falling asleep*	2.7 (1.1)	1.7 (1.1)
Sleep latency (min)*	30.5 (23.1)	12.1 (8.8)
Number of awakenings	3.1 (1.0)	2.6 (1.3)
Early awakenings	2.3 (1.4)	2.3 (1.6)
Quality of sleep*	2.7 (0.8)	2.0 (1.0)
Non-restorative sleep*	2.9 (1.4)	1.8 (1.2)
Daytime sleepiness*	3.1 (1.3)	1.4 (0.9)
Mean sleeping time	7.0 (1.3)	7.2 (1.0)
Frequency of naps	3.0 (1.5)	2.0 (1.2)

*$P < 0.05$, t-test.

Pain Rating Index was 18.5% (15.6%). The mean HAQ score was 6.1 (5.0). Medical treatment was second-line agents in 26 patients, 32 received analgesics and eight corticosteroids.

Controls were four men and 15 women, mean age 55.5 yr (17.5). All were healthy without any musculoskeletal symptoms and they had no complaints of pain, fatigue, sleepiness, etc.

For the subjective sleep complaints, selected data from the BNSQ are seen in Table I. Patients with RA had more difficulty falling asleep and more frequently felt that they had sleep problems. A 'non-restorative' sleep pattern and more daytime sleepiness were also seen in the patient group.

Polysomnography

Data from conventional sleep staging are seen in Table II. There was a tendency towards more stage shifts ($P = 0.07$) in the RA group and PML were more frequent among the patients ($P = 0.05$), but otherwise no significant differences were seen. When comparison of time spent in absolute minutes was made for the sleep stages (data not shown), the patients spent more time in stage NREM3 (44.8 *vs* 35.6 min; $P = 0.05$).

TABLE II
Selected sleep parameters in patients with rheumatoid arthritis and matched healthy controls. Values given as mean (S.D.). For definitions, see the text

	Rheumatoid arthritis	Controls
Time in bed (min)	438.2 (81.3)	435.8 (53.5)
Sleep period (min)	431.1 (51.2)	419.5 (56.4)
Total sleep time (min)	402.2 (48.8)	395.1 (63.7)
Sleep efficiency %	93.6 (7.4)	94.0 (5.3)
Wake %	9.6 (7.8)	8.8 (6.1)
NREM1 %	3.9 (2.6)	4.6 (2.4)
NREM2 %	46.6 (9.5)	48.0 (7.3)
NREM3 %	10.2 (5.2)	8.3 (2.9)
NREM4 %	11.2 (7.4)	12.1 (6.5)
REM %	18.7 (5.9)	18.3 (4.1)
NREM1 latency (min)	15.4 (12.4)	13.1 (9.5)
NREM2 latency (min)	6.1 (8.2)	7.0 (10.9)
NREM3 latency (min)	22.4 (12.5)	24.7 (17.9)
NREM4 latency (min)	50.3 (55.1)	41.3 (48.4)
REM latency (min)	97.0 (32.8)	98.1 (36.4)
No stage shifts	134.3 (143.2)	93.5 (26.2)
Arousal Index	9.1 (4.9)	7.7 (3.6)
Apnoea Index	2.1 (3.9)	1.0 (1.9)
PML Index	10.8 (16.3)*	4.1 (9.0)
Movement Index	7.9 (3.0)	6.7 (3.1)
Wake after sleep onset (min)	29.4 (36.0)	24.9 (20.7)
No. of awakenings > 2 min	3.0 (3.2)	2.4 (2.4)
No. of awakenings < 2 min	10.4 (6.3)	9.5 (3.9)

*$P < 0.05$, t-test.

When a subset of 17 patients having active disease was defined (fulfilling three of the following four criteria: number of swollen joints $\geqslant 3$, number of tender joints $\geqslant 6$, duration of morning stiffness > 45 min and erythrocyte sedimentation rate > 28), no differences in PSG parameters were observed in comparison with those patients having less active disease (data not shown).

Frequency analysis

In two subjects with RA and in one control, the technical quality of the recordings did not allow frequency analysis and they were omitted from the calculations. The distribution of power in the five

TABLE III
Normalized mean power in all frequency bands—delta (0.5–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), sigma (12–14.5 Hz) and beta (14.5–25 Hz)—in the sleep EEG (F1–A2 derivation) for sleep stages NREM1–4, NREM2–4 merged and REM

Stage		delta %	theta %	alpha %	sigma %	beta %
NREM1	RA	4.3 (1.5)	10.5 (2.3)	18.6 (5.2)	14.2 (3.4)	52.1 (8.7)
	N	5.2 (1.7)	11.6 (3.1)	17.7 (5.6)	13.1 (2.7)	52.4 (10.0)
NREM2	RA	8.2 (2.1)	16.8 (3.3)	23.9 (4.6)	15.3 (3.6)	35.5 (7.8)
	N	8.5 (2.4)	16.5 (3.3)	22.4 (4.6)	15.2 (2.9)	37.5 (9.1)
NREM3	RA	12.9 (3.5)	21.9 (3.9)	24.3 (5.0)	12.5 (3.3)	27.8 (6.1)
	N	13.2 (2.9)	22.0 (3.5)	22.1 (4.1)	12.2 (1.8)	30.5 (7.7)
NREM4	RA	17.1 (4.8)	24.3 (4.1)	21.8 (5.5)	10.8 (3.3)	27.7 (7.3)
	N	17.4 (4.4)	24.5 (4.4)	19.9 (4.2)	10.5 (2.2)	27.7 (8.0)
NREM2–4	RA	10.2 (2.9)	18.8 (3.9)	23.5 (4.3)	14.2 (3.4)	33.0 (8.0)
	N	10.7 (3.0)	18.5 (3.8)	21.7 (4.3)	14.0 (2.6)	35.1 (9.0)
REM	RA	7.1 (2.1)	14.2 (3.1)	18.3 (4.7)	12.5 (2.8)	47.6 (9.9)
	N	7.9 (2.0)	14.8 (3.5)	16.5 (4.4)	10.5 (2.2)	49.3 (10.0)

RA, patients with rheumatoid arthritis; N, normal subjects.

TABLE IV
Normalized mean power in all frequency bands—delta (0.5–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), sigma (12–14.5 Hz) and beta (14.5–25 Hz)—in the sleep EEG (F1–A2 derivation) for sleep cycles 1–4 in stages NREM2–4. For further explanation, see the text

Cycle	Stage		delta %	theta %	alpha %	sigma %	beta %
1	NREM2	RA	8.0 (2.3)	16.5 (2.8)	23.1 (4.1)	15.3 (3.5)	36.7 (6.3)
		N	8.8 (2.9)	16.9 (3.7)	22.3 (5.1)	15.1 (3.3)	37.0 (9.6)
	NREM3	RA	12.5 (3.8)	21.8 (3.0)	25.4 (6.0)	13.2 (3.6)	26.3 (5.4)
		N	12.9 (3.2)	22.2 (3.8)	22.8 (5.2)	12.5 (1.9)	29.7 (8.3)
	NREM4	RA	17.4 (5.3)	25.2 (3.9)	23.5 (5.7)	11.5 (3.2)	22.8 (4.4)
		N	17.8 (5.1)	24.9 (4.5)	20.2 (4.6)	10.6 (2.1)	26.5 (8.1)
2	NREM2	RA	8.5 (2.6)	15.1 (3.8)	24.3 (5.1)	17.6 (4.0)	34.1 (9.5)
		N	8.8 (2.5)	17.0 (3.7)	22.1 (4.9)	14.2 (2.5)	37.4 (9.6)
	NREM3	RA	12.9 (3.6)	12.2 (2.8)	23.7 (4.8)	22.3 (4.1)	28.6 (8.6)
		N	13.2 (3.8)	21.8 (4.1)	22.0 (4.3)	12.4 (2.6)	30.6 (7.8)
	NREM4	RA	16.7 (5.0)	10.5 (2.9)	20.8 (5.7)	24.2 (5.1)	27.1 (9.8)
		N	17.1 (4.0)	24.1 (4.8)	19.8 (4.5)	10.6 (2.9)	28.4 (10.7)
3	NREM2	RA	8.0 (2.6)	16.7 (4.3)	23.9 (5.5)	15.3 (3.9)	35.7 (10.7)
		N	8.5 (2.3)	16.9 (3.4)	23.1 (5.2)	15.1 (2.9)	36.3 (10.2)
	NREM3	RA	13.0 (2.8)	22.5 (3.5)	24.1 (5.6)	12.2 (3.0)	27.8 (7.3)
		N	12.4 (2.7)	21.9 (3.6)	23.3 (5.2)	12.4 (1.7)	29.9 (9.2)
	NREM4	RA	16.7 (3.6)	24.8 (3.4)	21.0 (3.9)	10.2 (2.6)	26.7 (5.9)
		N	15.6 (4.9)	23.3 (5.2)	20.1 (4.3)	11.1 (2.3)	29.9 (9.7)
4	NREM2	RA	7.3 (2.2)	16.6 (3.7)	24.9 (4.8)	15.5 (4.0)	34.9 (8.0)
		N	7.7 (2.9)	15.3 (4.5)	21.5 (5.7)	15.8 (3.6)	39.8 (12.6)

RA, patients with rheumatoid arthritis; N, normal subjects.

frequency bands was calculated for a total of ~700 000 2-s epochs (Table III). Patients with RA had more power in the alpha band in sleep stages NREM2–4 combined in comparison with controls ($F = 5.6$, $P = 0.02$), but no differences in power were seen in the other frequency bands. Data from the analysis in sleep cycles are shown in Table IV. For cycle 4, only six patients and three controls spent time in NREM3 and 4, and therefore data for these stages were omitted. Six controls and 15 patients slept in cycle 5, but due to the small number of epochs spent in this cycle (most of these subjects had their final awakening here), data were excluded from analysis. For individual sleep cycles, the patients had more alpha power in stage NREM2–4 in cycles 1, 2 and 4 [$F = 6.9$, $P = 0.01$; $F = 4.6$, $P = 0.03$ and $P = 0.05$ (t-test), respectively] and controls had more power in the beta band in cycle 1 ($F = 4.7$, $P = 0.03$).

The decline in total amount of delta power during sleep cycles followed the expected exponential curve [43] in both groups and no differences were observed. Total alpha power followed a more horizontal line, but again no significant differences were observed between the groups.

Correlations

Interactions between clinical and sleep variables in the initial model are shown in Fig. 1. As expected, significant associations were found between most clinical scores, and correlations were also demonstrated between several sleep variables. When the relationships between individual variables were taken into account, variables such as fatigue, HAQ, physical activity and sleepiness did not correlate with sleep parameters, and the individual frequency bands also showed very weak interactions with the other variables. Because of the relatively small amount of data in comparison with the many variables, the initial model was too unstable to draw any final conclusions on the relationships. The tendencies were, however, used in an objective selection of variables to be used in the final model, as stated in the Methods. After stability of the system was reached in the final model, many variables did not influence the system and these were excluded during processing. Furthermore, the relationship between some variables

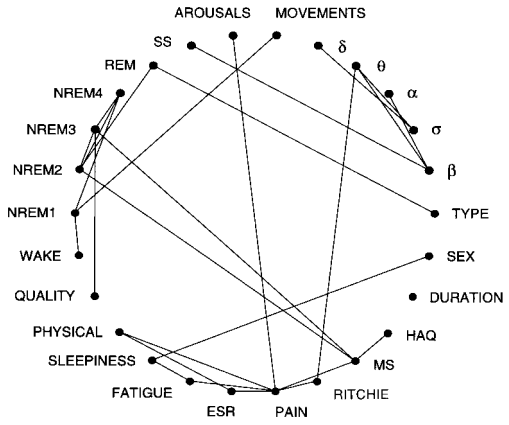

FIG. 1.—The 'initial' graphical chain model showing all variables where points connected by a line are related. Correspondingly, points which are not connected are conditionally independent. DURATION, duration of disease; MS, morning stiffness; ESR, erythrocyte sedimentation rate; PHYSICAL, physical activity index; QUALITY, subjective quality of sleep; SS, number of sleep stage shifts; δ, θ, α, σ and β refer to normalized power density in the respective frequency bands in NREM2–4 merged. For further explanations, see the text.

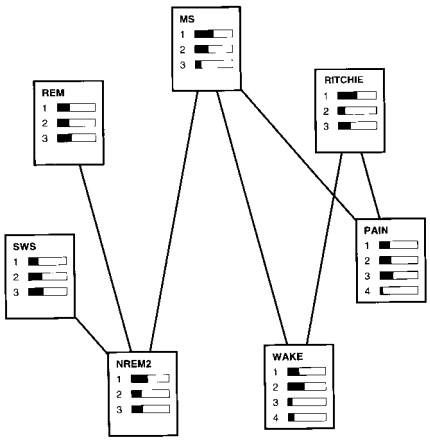

FIG. 2.—The final model, where data are presented using a causal probabilistic network shell. The black bars show the relative distribution of the variables (percentage) within the different levels (1–3/4), where an increasing value represents an increase in symptoms or time spent in a sleep stage. Values of the variables can be set at a given level and the distribution of the other variables changed correspondingly. Examples are given in Table V. MS, morning stiffness; RITCHIE, joint pain score; SWS, slow-wave sleep. For further explanations, see the text.

was modified after simplification of the model due to the information lost in the eliminated data (normally referred to as Simpson's paradox). The model found from the data is shown in Fig. 2 and Table V, first row. The two pain parameters were related to morning stiffness, which was shown to have a central role, being the most explanatory variable to predict the sleep profile. The interactions of the individual variables could then be studied dynamically using the CPN routines. The general impression was that an independent interaction between disease activity measured by morning stiffness, pain and Ritchie score on the one hand, and time spent in stage Wake, NREM2 and SWS on the other, exists. These findings are illustrated in the following simulated examples (Table V).

Example 1. A patient with maximal pain (=level 4). As seen in Table V (second row), a deterioration in morning stiffness and Ritchie score was seen (as expected) in comparison with the baseline distribution shown in the first row in Table V. A decrease in time spent in stage Wake and NREM2 was also observed with an increase in SWS. When the pain level was minimal, corresponding to level 1 (data not shown), a decrease in stage Wake was also seen, but SWS also decreased. Pain score at level 2 (not shown) was followed by an increase in time spent in stage Wake without major changes in SWS and stage REM.

Example 2. A patient with a high pain level as well as a long duration of morning stiffness (Table V, third row). The tendency in sleep parameters shown in the example above was further aggravated and especially time spent in SWS increased with a decrease in NREM2. Maximal morning stiffness

TABLE V

Relative distribution (%) of the variables shown in the final model shown in Fig. 2 (first row, baseline) and examples where simulated alterations are introduced in one or two parameters (underlined). Increasing level of a given variable represents an increase in symptoms or time spent in a sleep stage. For further explanation, see the text

Example	Level	Morning stiffness	Pain score	Ritchie score	Wake	NREM2	SWS	REM
Baseline	1	49	27	49	30	43	26	32
	2	35	30	19	43	27	36	31
	3	16	35	32	11	30	38	37
	4	–	8	–	16	–	–	–
1	1	0	–	0	33	64	25	33
	2	67	–	33	67	10	26	27
	3	33	–	67	0	26	50	39
	4	–	100	–	0	–	–	–
2	1	–	–	0	100	100	14	27
	2	–	–	100	0	0	18	23
	3	100	–	0	0	0	68	50
	4	–	100	–	0	–	–	–
3	1	–	0	–	0	100	14	27
	2	–	100	–	0	0	18	23
	3	100	0	100	67	0	68	50
	4	–	0	–	33	–	–	–
4	1	34	19	42	27	77	–	30
	2	37	30	21	42	8	–	26
	3	29	40	37	14	15	100	44
	4	–	11	–	17	–	–	–
5	1	64	45	64	100	36	27	32
	2	27	9	36	–	32	39	32
	3	9	36	0	–	32	34	36
	4	–	9	–	–	–	–	–

SWS, slow wave sleep.

alone caused the same alterations in sleep stages, and a decrease in morning stiffness resulted in a decrease in SWS (data not shown).

Example 3. A patient with a high Ritchie score and maximal morning stiffness is simulated in Table V, fourth row. As demonstrated, an increase in time spent in stage Wake was seen, but the alterations in stage NREM2 and SWS were comparable to those seen in the previous example. Correspondingly, an increase in Ritchie score alone increased only time spent in stage Wake (not shown).

Example 4. The effect of a change in sleep parameters. An increase in SWS only resulted in a slight increase in morning stiffness and an alteration in the two other sleep parameters (Table V, fifth row). An increase in SWS together with a decrease in REM, however, was correlated to a decrease in pain and morning stiffness (not shown).

Example 5. Finally, a decrease in stage Wake was followed by a decrease in pain level, Ritchie score and morning stiffness (Table V, sixth row).

DISCUSSION

Ambulatory recordings in non-selected patients with RA demonstrated an increase in the number of PML during sleep, but otherwise no major differences in classical sleep stages were observed in comparison with healthy controls. However, when sleep microstructure was studied, the patients had more alpha-EEG sleep. The graphical chain model showed a strong association between morning stiffness, pain and joint tenderness on the one hand, and sleep parameters, especially SWS and time spent awake, on the other, indicating important aspects of sleep/wake interactions.

Sleep macrostructure

Subjective sleep disturbances were prevalent in the patients. In RA, symptoms such as pain, fatigue and morning stiffness may be related to disturbances in the restorative functions promoted by sleep [10–12, 16, 44]. No major differences in sleep macrostructure, comparing patients and controls, were seen in this study, however. Although data are somewhat conflicting, most previous papers have reported normal sleep architecture (i.e. classical sleep stages) in RA. Sleep physiology, however, was found to be disturbed in these papers as fragmented sleep (awakenings and arousals), movements and apnoeas tend to be prevalent in the patients [9, 13, 15, 18, 20]. The tendency towards more stage shifts in the RA group seen in this report might indicate more fragmentation of sleep, but on the contrary no differences between the measures for arousals and awakenings were seen. In the current study, more PML were seen in the patients. This finding is in accordance with previous studies [9, 15, 20]. The clinical significance is unknown, but increased PML have also been found in various other medical disorders, and may be related to a central dopaminergic imbalance caused by the disease [9]. In comparison with previous reports, our patients had a higher sleep efficiency, spent more time in SWS and less time in stage Wake and NREM1. These findings can probably be attributed to the ambulatory sleep recordings, allowing the subjects to sleep in their natural settings, thus giving a more normal sleep pattern [29]. In some previous studies, patients were highly selected [13, 15, 18], most having a flare in the disease or suffering from severe fatigue. In comparison with these studies, our patients might have less activity of the disease. However, when the material was divided into those having more or less active disease, no differences were seen in the two groups. The same findings were observed in a previous questionnaire-based study [12]. These results can probably be related to the strong correlation between the clinical variables making the statistical evaluation difficult. This further emphasizes the value of graphical chain models in the analysis of such complex data.

Sleep microstructure

A quantitative increase in alpha-EEG was seen in sleep microstructure and findings were consistent in most sleep cycles. The alpha-EEG sleep, which is a relatively high-frequency activity superimposed on the normal EEG in NREM sleep stages [45], has been hypothesized to reflect an internal arousal activity interfering with the normal homeostatic functions during sleep [8, 21, 46–48]. Although seen in several medical and psychiatric disorders, alpha sleep has especially been associated with the fibromyalgia syndrome [46, 49]. In patients with RA where alpha sleep was prominent [13], this has been attributed to 'secondary fibromyalgia' co-existing with the primary disease. In the current study, however, none of the patients fulfilled the criteria for fibromyalgia [50] and the alpha sleep, being constant in most sleep cycles, seems also to be a prominent feature in RA. This has also been demonstrated in other studies [9, 15, 20], although no quantitative analysis was performed. Whether the alpha sleep reflects an internal arousal activity disturbing normal sleep or is a non-specific epiphenomenon [51] cannot, however, be concluded from this study.

Power in the delta band is probably the best single marker for the sleep process [43] and, among other abnormalities, a decrease in the normal exponential unwinding of power in the low-frequency range during sleep has been reported in fibromyalgia [38]. In RA, a normal decline of power in this band was seen and no disturbances in the sleep process were thus reflected. Therefore, sleep microstructure disturbances are probably more characteristic in patients with fibromyalgia than in RA. Although speculative, this may be related to different pain mechanisms in the two diseases. Thus, RA patients may have nociceptive inputs mainly from peripheral tissue interfering with sleep macrostructure. The pain in fibromyalgia, however, is thought to be of a more central origin [52], probably mostly reflected in sleep microstructure abnormalities.

Sleep/wake interactions

Statistical methods. Several statistical methods are available for the generation of hypotheses on associations between variables. For multiple parameters, the models most commonly used in medical research are based on ordinary multiple regression. In these models, an assumption of a linear relationship between the variables is made. Normal distribution of one variable, given the other, is also assumed. Where non-linearity exists, models such as curvilinear or logistic regressions [53] have been used. The relationship between biological variables, however, is often unknown or even more complex than assumed in the models above. Also, when more variables influence the structure of the system, the preliminary relationship between the variables is often not fulfilled during further analysis. In graphical chain models, no *a priori* assumptions on the distribution of data or the relationship between the variables are made. Instead, the models are based on a determination of the probability for a given association between two variables, when the influence of all the other variables in the model is taken into account. An advantage is the visual presentation of relationships between variables [40]. Nevertheless, this model also has limitations. Firstly, in the current case, a reduction to three levels was performed for variables with a continuous distribution, as for example the amount of time spent in a sleep stage. This was necessary to balance the number of data (i.e. subjects included) to the amount of variables. Secondly, active selection of variables was necessary to simplify the structure for a final interpretation of the results. However, this was mainly done on the basis of objective knowledge regarding the preliminary relationships which were found in the initial model.

Clinical variables and sleep. The interaction between the variables was rather complex, but all experiments in the model showed a tendency towards more time spent in SWS and less in NREM2, when a clinical deterioration was simulated. As time spent in stage REM is thought to be relatively independent of NREM stages, an increase in time spent in SWS will invariably change the relative amount of stage NREM2. NREM sleep stages, especially SWS, are thought to reflect restorative properties of sleep [3, 54–56]; therefore, the relationship between the clinical parameters and this stage is interesting. Thus, patients with high disease activity, reflected in morning stiffness, pain and joint tenderness probably need more SWS. Although questioned by Trachsel *et al*. [57], in experimental models of disease SWS seems important, being positively correlated with improved survival for example [58]. Correspondingly, an intimate relationship between the immune system and SWS has been hypothesized [59, 60]. Finally, in diseases where the release of cytokines (as in RA) is thought to play a role, a correlation between these substances and SWS has been reported [61, 62].

Pain and sleep disturbances may be intimately correlated and different sleep disturbances have been reported in association with pain. Thus, pain was reported to be a leading cause of insomnia in medical patients [4, 7], and previous studies in patients with rheumatic diseases have shown an association between pain, on the one hand, and awakenings, movements, alpha-EEG, decreased sleep efficiency and SWS on the other [7, 14, 19, 63–65]. Different sleep disturbances were also seen in patients with pain due to, for example, coronary heart disease [66–68]. In acute pain, e.g. in patients undergoing surgery, or in experimental pain in animals, fragmented sleep as well as a decrease in SWS and REM were reported, probably due to the pain and stress induced by the trauma [69–74]. The opposite effect on SWS in these studies and our findings may be explained by different mechanisms in acute and chronic pain. Epidemiological studies confirm an association between sleeping problems and pain [75], especially pain related to arthritis [76, 77]. On the other hand, sleep disturbances *per se* may also increase pain and stiffness, and selective SWS deprivation in healthy subjects has been shown to lower the pain threshold [8, 78]. Finally, in subjects with pain, decreased physical activity [7, 79], as well as psychological factors [76, 80–82], may contribute to the sleep disturbances, although pain itself seems to account for most of the variance in sleeping behaviour [7, 76]. Although pain was positively related to SWS in the current study, the strong interaction between the clinical variables must, however, be taken into account, and pain may also be considered as one of several measurements for disease activity. As demonstrated in Fig. 1, an association between pain level and arousals was also seen. However, the preliminary relationship was not sufficiently strong to persist when the selection of variables was performed to construct the final model. Sleep fragmentation, reflected in time spent in stage Wake (but not movements), was correlated to pain in the current model, but in a somewhat complex fashion. Moderate pain at level 2 increased time spent awake, whereas both maximal and minimal pain score decreased the time spent in this stage. An increase in Ritchie score, reflecting a more direct measurement for joint pain, was also correlated to increased time spent awake. Correspondingly, a decrease in Wake was followed by improvement in all clinical parameters. Whether pain affects time spent in stage Wake, or vice versa, cannot be concluded from this study, but both relationships probably exist.

Fatigue and sleepiness were not directly associated with sleep variables. This was surprising as fatigue is a major complaint in medical diseases [16, 26, 83, 84], and clinical as well as experimental studies have shown a close relationship between sleep fragmentation and daytime fatigue and sleepiness [16, 85–87]. However, as shown in Fig. 1, the relationship of fatigue and sleepiness to sleep disturbances may be mediated via variables such as pain and stiffness, and probably do not directly interfere with sleep architecture.

Medication

Medication may influence the sleep structure. A 2 week washout period was performed for antidepressants and/or benzodiazepines, but otherwise patients were on their normal medication. Corticosteroids especially have been thought to modify sleep and alterations in the normal ultradian secretion of this hormone may probably be caused by sleep disturbances. However, when a separate analysis of sleep parameters, as well as power in the individual frequency bands, was performed for patients receiving prednisone and those who did not, no systematic differences were found. This was supported by findings in a previous study in RA patients [15]. The heterogeneity in the consumption of analgesics and second-line agents in our material did not permit statistical analysis, but in previous studies in RA patients these drugs did not give changes in sleep structure [9, 20]. Therefore, we do not believe that medication influenced the results.

CONCLUSION

An increase in PML and the alpha-EEG were the only parameters distinguishing the ambulatory sleep recordings in patients with RA from those in healthy controls. However, significant relationships between morning stiffness, pain and sleep patterns were demonstrated, thus confirming the important interactions between sleep and daytime function in rheumatic diseases.

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