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ORIGINAL ARTICLE

Effect of anti-TNF treatment on sleep problems in ankylosing spondylitis

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Abstract Sleep disturbances and problems are increased in ankylosing spondylitis (AS). But much is not known in a quantitative way about sleep problems and effect of treatments on AS. This study is aimed first, to investigate sleep disturbances in AS and secondly, to evaluate the effects of anti-TNF treatment on SD in AS. One hundred seventy-one (Female/male: 90/81) AS patients fulfilling modified New York criteria and 86 (F/M: 56/30) age- and gender-matched controls without inflammatory diseases were included into the study. Demographic data and disease activity and treatments were recorded using *The Bath Ankylosing Spondylitis Functional Index* (BASFI) and *The Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI). The *Medical Outcomes Study* (MOS) Sleep Questionnaire was used for evaluating sleep and problems of sleep. AS patients had higher sleep disturbance scale (SDS) and sleep problem index (SPI) II scores. Group A (patients using NSAID and/or DMARD, 53.2% of patients) had higher BASDAI and BASFI compared with Group B (Patients using anti-TNF treatments) (4.29 ± 2.38 vs. 2.46 ± 2.32, $p < 0.001$; 1.95 ± 2.15 vs. 0.93 ± 1.31, $p < 0.001$, respectively). Whereas Group A had higher scores of SDS, awaken short of breath or headache, somnolence, and SPI-II than controls, none of the sleep parameters were statistically different between patients on anti-TNF treatments and controls. BASDAI was positively correlated with SPI-I, SPI-II, SDS, and somnolence scale. AS patients had increased sleep problems and disturbances compared with controls. Anti-TNF agents improve significantly these problems. Sleep problems are significantly correlated with the disease activity.

Keywords Sleep disturbances · Ankylosing spondylitis · Anti-TNF agents · MOS sleep index · BASDAI · BASFI

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Introduction

In addition to pain and stiffness, fatigue, and sleep problems are important concerns in patients with ankylosing spondylitis (AS) [1]. Various sleep problems including poor quality sleep, sleep onset insomnia, difficulty awakening, and obstructive sleep apnoea syndrome (OSAS) has been reported in AS [2]. The importance of fatigue in AS was already highlighted [3]. Fatigue and quality of life in AS is closely related to sleep disturbances (SD) [4].

Tumor necrosis factor-α (TNF-α) is major therapeutic target in AS [5] and there are several anti-TNF agents which significantly improve the signs and symptoms of AS [6, 7]. But much is not known in a quantitative way about the effect of treatments on sleep problems in AS.

This study is aimed first, to investigate sleep disturbances in AS and secondly, to evaluate the effects of anti-TNF treatment on SD in AS.

Patients and methods

Between January 2008 and 2009, consecutive AS patients fulfilling modified New York criteria [8] and giving informed consent from our university hospital rheumatology outpatient clinic were included into the study. Demographic data and disease characteristics [disease duration,

acute phase reactants (erythrocyte sedimentation rate, C-reactive protein, hemogram)] and treatments were recorded from hospital files. Disease activity in AS was assessed with *The Bath Ankylosing Spondylitis Functional Index* (BASFI) [9] and *The Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) [10].

As a control, 86 age- and gender-matched consecutive controls giving informed consent without inflammatory diseases were recruited. For both AS and control group, The *Medical Outcomes Study* (MOS) Sleep Questionnaire was used for evaluating sleep and problems of sleep [11].

Measurements

The Bath Ankylosing Spondylitis Functional Index (BASFI) consists of eight questions on daily activities and two additional questions that assess patients' ability to cope with everyday life. Each question is answered on 10-cm horizontal visual analogue scale (VAS). The VAS have no distinguishing marks except the words "easy" and impossible "impossible" at either end of the line to indicate the direction of the severity. The mean of ten scales gives in the BASFI score (0–10), with higher scores indicating more severe impairment.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a self-administrated questionnaire consisting of six questions relating to the five major symptoms fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, and morning stiffness, measured in terms of both severity and duration. The patients were asked to mark the degree to which they had experienced aforementioned symptoms over the previous week. Each of the first five questions are answered on 10-cm, unmarked, horizontal VAS, except fort the words "none" and "very severe" on the left and right ends, respectively, while the scale for duration of morning stiffness is graded every 15 min between 0 and 2 h. After converting the question on length of morning stiffness to 0–10, BASDAI is calculated with the formulae $[1 + 2 + 3 + 4 + ([5 + 6]/2)]/5$.

The *Medical Outcomes Study* (MOS) Sleep Questionnaire (Table 1) is a 12-item self-report questionnaire that yields 2 sleep problem indexes (SPI-I, 6 items and SPI-II, 9 items) and 6 scale scores: the sleep disturbance scale (SDS, 4 items), daytime somnolence (3 items), snoring (1 item), awaken short of breath or with headache (1 item), and quantity of sleep (1 item). Answers refer to a retrospective assessment over the past 4 weeks. The quantity of sleep is scored as the average number of hours slept per night. Except for the quantity of sleep measure, the MOS sleep scales and indexes are scored on a 0–100 possible range, higher scores indicating more sleep problems.

Statistical analysis

Statistical analysis was performed with SPSS 11.0 and statistical significance was set at p less than 0.05. Data are presented as mean ± SD or median (range). Student's t-test was used for comparison of parametric data and Mann–Whitney U test for nonparametric data. Correlation was tested using Pearson's correlation coefficient for parametric values and Sperman's correlation test for nonparametric values.

Results

One hundred seventy-one (Female/male: 90/81) AS patients and 86 controls (F/M: 56/30) were included into the study.

Table 1 Question concepts and associated sleep scales of the MOS scale

Questions	SDS	SNR	SOB	ADQ	SOM	SPI-I	SPI-II
Length of time to fall asleep	*						*
Hours slept							
Sleep was restless or tense	*						*
Enough sleep to feel rested				*		*	*
Awaken short of breath or with headache			*			*	*
Drowsy or sleepy during day					*		*
Trouble falling asleep	*					*	*
Trouble getting back to sleep	*					*	*
Trouble staying awake during day					*	*	*
Snoring		*					
Napping during day					*		
Get amount of sleep needed				*		*	*

SDS sleep disturbance scale, *SNR* snoring, *SOB* sleep short of breath or headache, *ADQ* sleep adequacy, *SOM* sleep somnolence, *SPI-I* sleep problem index I, *SPI-II* sleep problem index II

* Items taken into the sum score for each scale

Table 2 Demographic characteristics and disease activity parameters of 171 AS patients

Variable	Values
Ages, yrs	36.4 ± 11.1
Sex, % male	47.4
Disease duration, yrs	7.2 ± 8.7
ESR, mm/hr	9 (1–52)
CRP, mg/L	3.5 (1–9.4)
BASDAI	3.39 ± 2.52
BASFI	1.95 ± 2.15
Treatment	
NSAID and/or DMARD, *n* (%)	91 (53.2)
Anti-TNF agents, *n* (%)	80 (46.8)
Infliximab, *n*	47
Etanercept, *n*	22
Adalimumab, *n*	11

Variables are presented as mean ± standard deviation or median (range)

ESR Erythrocyte sedimentation rate, *CRP* *C*-reactive protein, *NSAID* Nonsteroidal anti-inflammatory drugs, *DMARD* Disease modifying antirheumatic drugs

Demographic characteristics, disease activity parameters, and treatments of AS patients were shown in Table 2.

Although there was no difference between AS patients and controls regarding ages and sex, AS patients had higher SDS and SPI-II scores (Table 3). There was no difference between the groups regarding snoring, awakening, sleep adequacy, and somnolence.

In subgroup analysis of AS patients according to the treatment, Group A (Patients using NSAID and/or DMARD treatment) had higher BASDAI and BASFI compared with Group B (Patients using anti-TNF treatments) (4.29 ± 2.38 vs. 2.46 ± 2.32, $P < 0.001$; 1.95 ± 2.15 vs. 0.93 ± 1.31, $P < 0.001$, respectively). Group A had higher scores of SDS, awaken short of breath or headache, somnolence, and SPI-II than controls. In the comparison of Group B and controls, none of the sleep parameters were statistically different between patients on anti-TNF treatments and controls (Table 4).

Correlation analysis of AS disease activity with sleep parameters

BASDAI was positively correlated with SPI-I, SPI-II, SDS, and somnolence scale ($P < 0.001$ and $r = 0.480$; $P < 0.001$ and $r = 0.548$, $P < 0.001$ and $r = 0.481$, $P < 0.001$ and $r = 0.481$, respectively). BASFI had positive correlation with SDS and somnolence scale ($P = 0.044$ and $r = 0.255$, $P = 0.001$, $r = 0.41$) ESR was positively correlated with SDS ($P = 0.04$ and $r = 0.277$).

Discussion

This is the first study assessing sleep from several perspectives as disturbance, snoring, somnolence, adequate sleep, and awakening in AS. Additionally, effects of treatments on these parameters were investigated. Our results showed that even though AS patients had increased sleep disturbances and sleep problems compared with controls, no significant difference was found between patients using anti-TNF agents and controls.

Although sleep problems are common in the general population, pain conditions, chronic illness, and mood disorders are associated with increased sleep disturbance [12]. In parallel to previous studies [4, 13], our AS patients had increased sleep problems and disturbances than controls. Sleep disturbance was clearly correlated with disease activity measured with BASDAI and BASFI. Moreover, it was correlated with ESR. Patients on NSAID and/or DMARD treatment had higher disease activity so, sleep problems, disturbances, and awakening.

As it was to be expected, treatments that improve AS clinical status also reduce sleep disturbance. For none of the sleep parameters that was a statistically significant difference between patients on anti-TNF treatments and

Table 3 Sleep abnormalities in patients with AS and controls

Variable	AS patients ($n = 171$)	Controls ($n = 86$)	*P*
Ages, yrs	36.4 ± 11.1	38.4 ± 9.6	>0.05
Gender, male (%)	47.4	34.9	>0.05
Sleep disturbance scale, 0–100	**43.9 ± 27.7**	**33.5 ± 28.4**	**0.006**
Snoring	33.3 ± 35.1	32.1 ± 39.1	>0.05
Awaken short of breath or headache	21.1 ± 25.2	14.9 ± 25.3	>0.05
Sleep adequacy	44.9 ± 25.8	48.3 ± 27.6	>0.05
Sleep somnolence	33.5 ± 22.9	28.8 ± 23.2	>0.05
Sleep problem index I, 0–100	36.8 ± 19.4	33.7 ± 20.5	>0.05
Sleep problem index II, 0–100	**39.7 ± 19.7**	**34.0 ± 20.2**	**0.034**
Hours slept	6.91 ± 1.67	6.74 ± 1.32	>0.05

Variables are presented as mean ± standard deviation

Statistically significant values are indicated in bold

Table 4 Comparison of AS subgroups and controls

Variable	Group A ($n = 91$)	Group B ($n = 80$)	Controls ($n = 86$)	P_1	P_2
Ages, years	34.5 ± 12.1	37.4 ± 10.4	38.4 ± 9.6	>0.05	>0.05
SDS, 0–100	**47.2 ± 27.9**	40.3 ± 27.2	**33.5 ± 28.4**	**0.002**	>0.05
Snoring	28.4 ± 31.2	38.8 ± 38.4	32.1 ± 39.1	>0.05	>0.05
Awaken short of breath or headache	**22.4 ± 24.7**	19.5 ± 25.9	**14.9 ± 25.3**	**0.047**	>0.05
Sleep adequacy	46.8 ± 25.9	42.7 ± 5.6	48.3 ± 27.6	>0.05	>0.05
Sleep somnolence	**36.8 ± 24.0**	29.9 ± 21.1	**28.8 ± 23.2**	**0.026**	>0.05
SPI-I, 0–100	39.2 ± 19.9	34.2 ± 8.5	33.7 ± 20.5	>0.05	>0.05
SPI-II, 0–100	**42.5 ± 19.9**	36.5 ± 19.0	**34.0 ± 20.2**	**0.005**	>0.05
Hours slept	6.9 ± 1.7	6.8 ± 1.6	6.7 ± 1.3	>0.05	>0.05

Variables are presented as mean ± standard deviation

Group A using NSAID and/or DMARD, *Group B* using anti-TNF agents, *P1* (group A vs. control), *P2* (group B vs. control), *SD.* sleep disturbance scale, *SPI-I* sleep problem index I, *SPI-II* sleep problem index II

Statistically significant values are indicated in bold

controls. There are observations that etanercept and infliximab could reduce daytime sleepiness in RA [12]. In an efficacy and safety study of golimumab in AS patients, a decrease in sleep disturbance by 3 unit on a 0–20 units scale assessed with Jenkins sleep disturbance scale was shown [14]. We found that using anti-TNF therapy could decrease not only sleep disturbances but also awakening and other sleep problems.

OSAS was found more prevalent in AS than in the general population (11.7–22.5% vs. 1–4%) in previous studies [15, 16]. In our study, there was no difference between AS and controls regarding snoring, somnolence, and awakening. But patients on NSAID and/or DMARD treatment had higher somnolence and awakening. It was shown that 41% of AS patients complaining fatigue, awakened more than 3 times each night [2]. Increased awakening by short of breath could be a result of costochondral and back pain due to disease activity of AS. Anti-TNF treatment could improve somnolence and awakening. Effect of anti-TNF treatment on OSAS in AS patients should be investigated with further studies using polysomnography.

In our study, we had used MOS sleep indexes and scales. But administration and scoring of MOS questionnaires are very difficult [11, 12]. On the other hand, BASDAI is moderately correlated with sleep problem index II and sleep disturbance scale. It is not surprising that patients with increased disease activity (measured with BASDAI) would have more sleep problems and disturbances.

Conclusion

Our data indicate that disease activity plays an important role in sleep disturbance in AS. Anti-TNF agents improve sleep problems in addition to other symptoms of AS.

Conflicts of interest None

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