

Sleep Disturbances in Patients with Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Sleep problems are frequent in chronic diseases like rheumatoid arthritis (RA). The present study was conducted to determine frequency of sleep disturbances and their relations with disease severity.

METHODS: The present case-control study was performed on 100 rheumatoid patients who were referred to the rheumatology clinic at the Avicenna hospital. A hundred age- and sex- matched healthy individuals were recruited in the study as a control group. Pittsburgh Sleep Quality questionnaire, Insomnia Severity Index questionnaire and Epworth Sleepiness Scale were used. The disease activity was calculated with the disease activity score 28. The collected data were analyzed using SPSS version 19.

RESULTS: Mean scores of the sleep quality were 6.2±4.3 in patients and 4.6±2.5 in control group. 28% of the patients had good sleep quality whereas 72% had poor sleep quality. Daytime sleepiness was present in 24.8% of the patients and 15% of the control group. Multiple logistic regressions showed that insomnia, pain and disease intensity were the most important factors that determine patients' sleep quality.

CONCLUSION: The present study showed that sleep disturbances are frequent in patients with RA and may contribute to disease severity. It is recommended that rheumatoid patients be evaluated for sleep disturbances during routine examinations.

KEY WORDS: Rheumatoid arthritis, Sleep quality, Insomnia, Daytime sleepiness

complained of morning stiffness, fatigue, and diffuse weakness. Some studies have also shown that sleep disturbances are commonly seen in patients with RA^{6,7}.

Sleep disturbances in these patients is associated with several causes. One of the causes is disease-related conditions such as anxiety and depression. Other causes of sleep disturbances are pain and physiological conditions of disease such as need to get out of bed to urinate frequently. Primary sleep disturbances such as sleep apnea or primary insomnia is also another cause of sleep disturbances and induces poor quality of sleep in these patients. Moreover, bad night's sleep and sleep disturbances result more patient's main symptoms^{8,9}. In case of infectious and autoimmune diseases like RA, it is believed that the causes of sleep disturbances in these patients are beyond the pain intensity. Pathological changes induced by the disease can be the cause of sleep disturbances in these patients.

For many years it was determined in infectious diseases that bad night's sleep can have bad impacts on health, well-being and sense of the physiological parameters. Moreover, it is known that the systemic infection directly cause sleep disturbances by cytokines and microbial production¹⁰⁻¹³. However, understanding of the relationship between sleep and immune function is still in its infancy.

Cytokines are key factors in the regulation of humoral immunity in humans. Animal studies have shown that several cytokines are effective in inducing sleep in animals. For example, interleukin-1 (IL-1), tumor necrosis factor and alpha interferon cause slow wave sleep in animals. IL-6 is also increased in plasma during waking. In human studies the relationship between sleep and immune mechanisms, such as cytokines, neuropeptide and neurotransmitters have been shown^{14,15}.

In most studies that have been performed so far, presence of sleep disturbances in a range of rheumatologic disease including systemic lupus erythematosus, fibromyalgia, chronic fatigue

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INTRODUCTION

RA is an autoimmune inflammatory disease with pain and swelling in joints and has a broad range of systemic manifestations¹. The disease is characterized by persistent inflammatory symmetrical synovitis in peripheral joints. Aetiology of the disease is unknown but it is believed that genetic vulnerability combined with environmental factors play a role in the disease^{2,3}.

Various infectious agents including Epstein-Barr virus, cytomegalovirus, mycoplasma are environmental factors involved in etiology of the disease^{4,5}. In addition, patients with pain and swelling of joints have also

syndrome, multiple sclerosis and RA have been investigated while a number of other studies have only examined patients with RA⁶. In a study conducted by Wolfe and associates, sleep disturbances and disease severity were investigated in a large number of rheumatoid patients and compared with control group. The prevalence of sleep disturbances were 45% in patients and 25% in controls, respectively. Sleep disturbances in patients were associated with pain and depressive symptoms and RA disease activity¹⁶. Similar results were obtained by Power and associates in 2005. In this study the prevalence of insomnia and non-hypnotic sleeping that induced with pain and other symptoms of rheumatoid disease were seen in 25% and 12% of patients respectively. These numbers are significantly higher than the control groups¹⁷.

Considering the importance of sleep disturbances in RA disease based on previous studies, the present study aim to investigate the prevalence of several kinds of sleep disturbances and their relationship with pain severity in RA patients.

MATERIALS & METHODS

The present investigation is a case - control study of RA patients who were referred to the rheumatology clinic of the Avicenna Hospital, Qazvin University of Medical Sciences. All patients were examined by a rheumatologist, and according to the revised criteria of the American College of rheumatology (ACR) (18) were diagnosed to have had RA. The inclusion criteria in this study were as follows: Patients of both sexes aged 20 to 80 whose diagnosis has at least passed one year. Exclusion criteria were: patients with chronic diseases, psychiatric disturbances, and known sleep disturbances. Patients who had been taking medications other than RA medication were also excluded. During the study period, 136 patients with RA were referred to the Avicenna Hospital's rheumatology clinic. According to the inclusion and exclusion criteria, a total of 100 patients with RA were enrolled in the study. The same number of people of matched sex and age constituted a control group who were primarily from the patients' accompanying persons and the same exclusion criteria were also considered in their enrollment.

The first part of the questionnaire was related to demographic data including age, gender, and questions about education and habitual snoring during night. The questionnaire contained questions to assess the presence of insomnia, daytime sleepiness and sleep quality in patients that were answered during an initial interview.

Sleep quality data were collected by the Pittsburgh Sleep Quality questionnaire. The attitude of the patients about their sleep quality during the past 4 weeks was assessed in 9 questions. Based on the answers, scoring was performed in seven parts, each from 0 to 3 points and the sum total score were obtained between 0 and 21. An overall score greater than 5 would mean poor sleep quality¹⁹. In the next section, the level of sleepiness during the day was measured by Epworth sleepiness scale (ESS). The questionnaire consisted of eight questions to bring up situations in which individuals might unwantedly fall asleep. Each question had a score of 0 to 3. If the sum was greater than 10, it would indicate excessive daily sleepiness whereas below this number would be considered normal.

The Insomnia Severity Index (ISI) used in the study comprises seven items assessing problems with sleep onset, sleep maintenance, and early morning awakening, interference of sleep problems with daily functioning, and perceived prominence of impairment related to the sleep problem, concern about sleep problems, and satisfaction with sleep patterns. Each item can be rated on a scale of 0 to 4 and a total sum of 0 to 28 can be obtained from adding the given scores up²¹.

In the present study the rate of disease activity was measured based on DAS28 Criterion: 1. Number of swollen joints 2. Number of tender joints 3. ESR 4. patient's general health²².

Reduced efficiency in patients was assessed with regard to the functional class used in patients with RA²³.

The data were analyzed using SPSS software version 19. Quantitative and qualitative values were expressed as means and percentages respectively. Statistical methods such as T-Test, chi square test and Pearson correlation analysis were utilized to analyze the relationships between the variables.

RESULTS

In this study, 100 patients with RA and 100 healthy individuals as healthy controls were enrolled. Demographic characteristics of patients and controls are shown and compared in Table 1. As seen in table 1, there is no difference between the patient and control groups in terms of demographic variables. The average severity of disease according to DAS28 was 3.13 ± 1.2 and average of patient's ESR was 20.2 ± 15.8 . According to functional class assay, 58 patients were classified in group one and 28, 10 and 4 patients were in group 2, 3

and 4 respectively. The average of VAS number, as a severity of pain, was 33.04±40.6.

Table 1- Clinical and socio-demographic parameters among patients and controls

Variables	RA Patients	Controls	P-value
Age	49.5±12.1	48.9	0.72
Gender			-
Male	10	10	
Female	90	90	
Body mass index	28.8±5.8	27.2±4.7	0.07
Marriage			0.39
Single	5 (5%)	8 (8%)	
Married	95 (95%)	92 (92%)	
Education	6.8±5.6	9.4±6.1	0.02
Excessive daytime sleepiness	6.8±2.1	5.2±3.2	0.07
Insomnia (global score)			
Difficulty in initiating sleep	51 (51%)	32 (32%)	0.04
Difficulty in continuity sleep	54 (54%)	42 (42%)	0.11
Early morning awakening	35 (35%)	22 (22%)	0.009
Snoring	35(37%)	26 (26%)	0.75

Table 2- Comparison of results from different subscales of

Pittsburg Sleep Quality Index among RA patients and controls

Variables	RA Patients	Controls	P-value
PSQI global score	6.2±4.3	4.6±2.5	0.003
Subjective sleep quality	0.8±1.1	0.6±0.9	0.02
Sleep onset latency	0.9±1.2	0.5±0.8	0.005
Sleep duration	0.7±1.1	0.8±0.8	0.07
Habitual sleep efficiency	0.8±0.7	0.6±0.6	0.08
Sleep disturbances	1.1±0.6	0.7±1.1	0.006
Use of hypnotic drugs	0.7±0.3	0.6±0.5	0.09
Daytime dysfunction	0.9±1.4	0.8±1.2	0.1

Table 2 has compared results of the Pittsburgh Sleep Quality questionnaire in two groups of patients and controls. As seen in Table 2, patients have higher score than the control group, in most areas of the Pittsburgh questionnaire. In examining the relationship between insomnia severity and disease severity according to DAS28 it was shown that with increasing severity of disease, insomnia increases significantly in patients ($\rho=0.2$, $P=0.02$). Likewise, the increasing severity of the disease was shown to have an impact on worsening of sleep quality ($\rho=0.4$, $P=0.01$). There was no correlation between the severity of the disease and daytime sleepiness in patients. Similar results were observed between pain intensity according to VAS assay and severity of insomnia and sleep quality, respectively ($\rho=0.6$, $P=0.005$ and $\rho=0.5$, $P=0.001$). But no relationship was observed between pain intensity according to VAS and daytime sleepiness.

Results from regression logistic analysis showed that the severity of the disease according to DAS28 (OR = 3.2, 95% CI: 1.5-3.9), and pain according to VAS (OR = 2.5, 95% CI: 1.2-2.9) were associated with poor quality of sleep. Also sleep onset insomnia (OR = 2.1, 95% CI: 1.2-2.9) and sleep-maintenance insomnia (OR = 1.8, 95%

CI: 1.1-2.4) were also associated with poor quality of sleep in patients.

DISCUSSION

The results of the present study suggested that the prevalence of poor sleep quality in RA patients was higher than the control group. Also, sleep quality was associated with severity of illness and intensity of pain, so that with increasing severity of illness and pain, sleep quality of patients was worse. Recent studies have shown that sleep disturbances is a major complaint in patients with RA and fatigue observed in these patients are due to poor sleep, functional disability, joint pain and depression^{6,5,24-25}. Studies in the general population have shown a relationship between inflammation and changes in the normal sleep pattern, so that patients with inflammation of various reasons suffered from sleep disturbances more. In addition the poor quality and disturbed sleep can worsen the symptoms and pain²⁶.

Taylor and colleagues in Canada in 2011 have shown that there is disturbances in beginning of sleep and sleep quality in patients with RA. In this study, patients had more difficulty at the beginning of sleep and waking up early in the morning than those of the control group and this difference was statistically significant, but patients have no difficulty in terms of waking up frequently during the night²⁷.

Regression analysis in this study showed that the most important factors causing poor quality of sleep are insomnia in patients and also the pain and disease severity. This suggests that proper management of pain in patients with arthritis may improve sleep quality in patients. In a large cohort study by Sutton and his colleagues on Canadian population a statistically significant and independent association was shown between incidence of insomnia and pain in rheumatic diseases²⁸.

Wilcox and colleagues have shown that there is no significant correlation between pain and sleep disturbances in patients with non-inflammatory diseases of knee such as arthritis. This different result may be due to the study design because in this study those who had reported pain on most days of the week had been enrolled. The result can also be attributed to the role of immune system in creation sleep disturbances in rheumatoid patients.²⁹ As discussed in the introduction, there is a relationship between sleep disturbances and immune system mediators in human. A range of sleep

disturbances in diseases such as lupus, ankylosing spondylitis and fibromyalgia has been demonstrated^{30,31}.

John Gjevre and his colleagues in Canada in 2012 have shown that ESS score on 10 patients demonstrate abnormal drowsiness while in our study no abnormal ESS score was seen. In that study 68 percent of participants had abnormal Apneahypopnea index (AHI). Sleep apnea can be attributed to characteristics of disease itself and problems in temporo-mandibular and chorio-artinoid joints and cervical spine. But in our study there was no significant difference in terms of snoring among the two groups (P: 0.75)³².

Similar results were obtained by Stephanie et al in 2009. Proper control of the disease in patients with RA according to the test results show that there is no temporo-mandibular problem that leads to breathing difficulties³³. In their study sleep quality was shown to be associated with factors such as inflammatory disease process, joint pain and stiffness, the effects of medications and psychological factors such as depression and anxiety, menopausal status in women, physical activity and obesity. Our study also confirmed the relationship between pain and sleep quality³³. Report by Luyste et al in 2011 showed that worse sleep quality is associated with higher pain and patients with higher VSA have more complaint of insomnia³⁴. In our study the sleep quality was worse in patients with higher VSA (P: 0.001). In another study by Slatkowsky-Christensen et al, in 2007 most patients had difficulty in falling asleep and suffered from early waking up so that they woke up sooner than family members and subsequently they felt weak. Various reasons including effects of drugs on sleep, depression and pain can cause insomnia and complaints such as difficulty in falling asleep and early waking up in the morning³⁵. In a study by C Lee Yvonne et al in 2009 sleep problems were associated with pain². Similar results in this study suggest that sleep problems such as frequent awakening were higher in those with higher VSA.

In summary, based on results, it was found that insomnia and poor quality sleep are highly prevalent in patients with RA that enhance with increasing severity of the disease.

Accurate Treatment and proper control of patients will reduce these disturbances. Also, patients should be monitored for these disturbances. In addition, right-time diagnoses and proper control and treatment of these

disorders help to control the disease. Questionnaire to assess patients' sleep problems was a major limitation of the study whereas objective methods such as polysomnography and octygraphy may be obtain a more accurate result. Depression in patients was considered with only one question using patient histories to exclude patients with psychiatric disorders. Patients were examined by a psychiatrist to obtain reliable results.

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