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Anxiety, sleep quality and their relationship with inflammation in Takayasu's Arteritis

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Abstract

This study aimed to investigate anxiety, sleep quality, and their relationship with inflammation in patients with Takayasu's arteritis (TA). Twenty-four patients diagnosed with TA and sex and age matched healthy controls were enrolled in the study. The quality of sleep was evaluated by Pittsburgh sleep quality index (PSQI), and anxiety were assessed by The Spielberger State-Trait Anxiety Inventory and Hamilton Anxiety Rating Scale. The disease activity was evaluated with sedimentation and C-reactive protein (CRP). The levels of anxiety and overall PSQI scores were significantly higher in TA than in healthy controls. Sleep disturbance was identified in half of the TA patients. The presence of systemic findings, CRP, and all subscale items of the Hamilton Anxiety Rating Scale and Spielberger State-Trait Anxiety Inventory were found to be higher in TA patients with poor sleepers compared to good sleepers. There was a significant correlation between all components of PSQI and anxiety scores. The present study has demonstrated higher anxiety scores and poor sleep quality among patients in TA compared with healthy controls. TA patients with systemic findings and high inflammation should be evaluated for poor sleep quality. Also, remission in disease activity may be associated with better sleep and less anxiety scores.

Keywords: Takayasu's arteritis, anxiety, sleep quality, inflammation

1. Introduction

Takayasu's arteritis (TA) is a chronic granulomatous large-vessel arteritis predominantly affecting the aorta and its main branches (1). The inflammatory process of TA causes thickening, narrowing, occlusion of the affected vessels and finally results in various symptoms such as dizziness, upper limb intermittent claudication, aortic regurgitation, and retinopathy (1). Mortality and morbidity are generally related to ongoing inflammation and ischemia (1, 2).

Chronic vascular inflammation may cause morbidity as it affects the quality of life and functional status. In particular, in systemic vasculitis, health-related quality of life decreased at physical, social, and emotional levels and impaired compared to the general population (3, 4). Recent studies have suggested that quality of life parameters are impaired in small to medium vessel systemic vasculitides and also in TA (5). A study demonstrated that the quality of life including both physical and mental components was lower in TA patients than in healthy controls (6).

Depression and fatigue affect the quality of life with the social burden (7). Depressive disorders may be seen in many rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (SjS), and ankylosing spondylitis (8). The anxiety, depression, and fatigue scores were higher in SjS compared to healthy individuals (9, 10). Depression and high disease activity scores appear to be predictors of low sleep quality in RA patients (11). In patients with SLE, pain and fatigue are associated with sleep disorders (12). The psychosocial, psychological factors, and especially depression were reported as possible factors for sleep disorders in these patients (12). It has been reported that impaired quality of life, depression, and anxiety are more common in patients with TA (13).

To our knowledge, limited studies about anxiety, sleep quality, and their relationship with inflammation in patients with TA were presented. Our aim is to investigate the association between sleep quality and anxiety in the study. We also evaluated the relationship between inflammation markers with sleep quality and anxiety.

2. Materials and Methods

2.1. Patients enrollment

A total of 24 patients with TA and sex and age matched healthy subjects without any diseases were enrolled in this cross-sectional study in a single institution. All the patients

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fulfilled the 1990 American Society of Rheumatology classification criteria of TA (14). The study protocol was approved by the Faculty of Medicine Ethics Committee and designed consistent with the Declaration of Helsinki (approval number 2021/5). Written informed consent was obtained from all subjects. The clinical and laboratory characteristics such as age, sex, smoking, alcohol, medication, disease duration, presence of systemic findings, occupation, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were evaluated. The disease activity of TA was evaluated with ESR and CRP.

2.2. Measurement of sleep quality: Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality over a 1-month time interval. Seven components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction were evaluated. A global score (range: 0 to 21) was obtained from the components (15). Patients with a total score>5 are defined as poor sleepers.

2.3. Measurement of anxiety: The Hamilton Anxiety Rating Scale

It was used to measure the severity of perceived anxiety symptoms with 14 symptom-defined elements and caters to both psychological and somatic symptoms. Each item is scored on a basic numeric scoring of 0 (not present) to 4 (severe), and 0-7=no/minimal anxiety; 8-14=mild anxiety; 15-23=moderate anxiety; and 24 or greater=severe anxiety (16).

2.4. Measurement of anxiety: The Spielberger State-Trait Anxiety Inventory

The Spielberger State-Trait Anxiety Inventory (STAI) was used to assess the degree of anxiety with 2 subscales as state anxiety (STAI-S) and trait anxiety (STAI-T) (17). The statements in the inventory are rated from 1 to 4 according to how much of each item the individual is currently feeling (STAI-S) or how often each item is felt (STAI-T). The total scores range from 20, which reflects the lowest possible degree of anxiety (state or trait), to 80, the highest possible anxiety score (17).

2.5. Statistical analysis

Data statistics were analyzed with Statistical Package for Social Sciences (SPSS) for Windows (SPSS version 20.0, IBM, USA). The data were expressed as mean±standard deviation, median [25p-75p], frequency (n), and percentage (%). Kolmogorov-Smirnov test was used to determine the distribution of normality. The Student's t-test and Mann-Whitney U test were used to compare differences between two independent groups according to the distribution of normality. The chi-squared test and Fisher's exact test were used for the analysis of categorical data and independence between variables. Pearson/Spearman's correlation analyses were used to evaluate the relationship between two continuous variables. A p-value of less than 0.05 was considered statistically significant.

3. Results

A total of 24 patients with TA and age-sex matched healthy groups were included in the study. The mean age of patients with TA was 40.5±15.3 years, it was 39.2±12.4 years for the healthy group. The majority of the patients were female. The ratio of unemployed and employed patients was 6 (25.0%) and 18 (75.0%), respectively. 79.2% of the patients had systemic findings. There were no significant differences in age, gender, marital status, occupation, smoking, alcohol taking, and psychiatric medication between both groups. The mean ESR was 59.8±25.8 mm/h and the median CRP was 26.9 [6.5-35.8] mg/L, respectively. All patients were taking a corticosteroid, methotrexate, azathioprine, tocilizumab, or their combinations. Demographic, clinical, and laboratory characteristics of patients with TA are shown in Table 1.

Table 1. Demographic, clinical, and laboratory characteristics of patients with Takayasu arteritis

Demographic Parameters	Takayasu arteritis (n=24)	Healthy Group (n=24)	p
Age (years)*	40.5±15.3	39.2±12.4	NS
Gender n (%) Male Female	 2 (8.3%) 22 (91.7%)	 2 (8.3%) 22 (91.7%)	NS
Disease Duration (months)*	29.7±18.3	-	
Marital status n (%) Alone Marriage/family	 4 (16.7%) 20 (83.3%)	 8 (33.3%) 16 (66.7%)	NS
Occupation n (%) Employed Unemployed	 6 (25.0%) 18 (75.0%)	 10 (41.7%) 14 (58.3%)	NS
Smoking n (%) Yes No	 4 (16.7%) 20 (83.3%)	 7 (29.2%) 17 (70.8%)	NS
Alcohol n (%) Yes No	 1 (4.2%) 22 (95.8%)	 3 (12.5%) 21 (87.5%)	NS
Psychiatric Medication n (%)	6 (25.0%)	3 (12.5%)	NS
Presence of Systemic Findings n (%)	19 (79.2%)	-	
ESR (mm/h)*	59.8±25.8	17.2±14.7	**<0.001**
CRP (mg/L)**	26.9 [6.5-5.8]	2.0 [2.0-2.3]	**<0.001**

*mean± standard deviation; **median [25-75p]; ESR, erythrocyte sedimentation Rate; CRP, C-reactive protein; NS: not significant

The median psychological and somatic Hamilton Anxiety Rating Scale scores were 5.0 and 5.5 in patients with TA. 12.5% of the patients had moderate-severe anxiety and 4.2% of patients had severe anxiety. In the patient group, the mean state anxiety and trait anxiety scores were 43.9±6.9 and 45.7±8.6, respectively. When the patients and control groups were compared in terms of anxiety with STAI and Hamilton

Anxiety Rating Scale, the scores were significantly higher in patients with TA compared to healthy control (Table 2).

The PSQI scores for subjective sleep quality (p=0.01), sleep efficiency (p=0.002), sleep disturbance (p=0.003), daytime dysfunction (p=0.01), and overall score (p=0.003) were significantly higher in patients with Takayasu arteritis compared to the controls (Table 2). According to the PSQI, 12 (50.0%) of the patients with Takayasu arteritis and 3 (12.5%) of the healthy controls were classified as poor sleepers. There were significant differences in CRP, presence of systemic findings, Hamilton Anxiety Rating Scale score, STAI-S score, and STAI-T score. However, no significant differences were found in age, gender, marital status, occupation, smoking, alcohol, and ESR between poor and good sleepers in TA.

Table 2. The distribution of anxiety scales and Pittsburgh sleep quality index in patients with Takayasu arteritis and healthy controls

Variable	Takayasu arteritis (n=24)	Healthy Group (n=24)	p
Anxiety Status*			
Mild	12 (50.0%)	7 (29.2%)	
Moderate to severe	3 (12.5%)	-	**0.01**
Severe	1 (4.2%)	-	
Hamilton Anxiety Rating Scale Score**			
Psychological	5.0 [3.0-6.0]	2.0 [0-3.0]	**<0.001**
Somatic	5.5 [3.0-8.75]	1.0 [0-4.75]	**0.001**
Spielberger State-Trait Anxiety Inventory Score***			
State Anxiety	43.9±6.9	33.6±9.9	**<0.001**
Trait Anxiety	45.7±8.6	35.1±12.2	**0.001**
Pittsburgh sleep quality index			
Sleep latency	1.0 [0-2.0]	0 [0-1.0]	0.06
Sleep efficiency	0 [0-1.0]	0 [0-0]	**0.002**
Sleep duration	1.0 [0-1.0]	0 [0-1.0]	0.11
Sleep disturbance	1.0 [1,0-1.0]	1,0 [0-1.0]	**0.003**
Sleep medication	0 [0-0.75]	0 [0-0]	0.51
Daytime dysfunction	1.0 [0.25-2.0]	0 [0-1.0]	**0.01**
Subjective sleep quality	1.0 [0.25-1.0]	0 [0-1.0]	**0.01**
Overall score	5.5 [3.0-9.0]	0 [0-5.0]	**0.003**

*Hamilton Anxiety Rating Scale n (%); **median [25-75p]; ***mean±standard deviation

The PSQI scores for subjective sleep quality (p=0.002), sleep latency (p=0.004), sleep duration (p=0.02), sleep efficiency (p=0.02), sleep disturbance (p=0.03), daytime dysfunction (p=0.02), and total score (p<0.001) were significantly higher in poor sleepers than good sleepers. The comparison of patients' characteristics between good and poor sleepers are shown in Table 3.

Table 3. The comparison of patient characteristics between good and poor sleepers in patients with Takayasu Arteritis

	Poor sleeper (n=12)	Good sleeper (n=12)	p
Age (years)*	41.4±16.9	39.5±14.2	0.77
Gender (M: F)	1:11	1:11	1.00
Disease Duration (months)*	25.7±19.2	33.8±17.2	0.29
Presence of Systemic Findings n (%)	12 (100%)	7 (58.3%)	**0.03**
Education Status n (%)			
Less than high school	5 (41.7%)	6 (50.0%)	
High School	4 (33.3%)	6 (50.0%)	0.28
University	3 (25.0%)	-	
Marital status n (%)			
Alone	3 (25.0%)	1 (8.3%)	0.59
Marriage/family	9 (75.0%)	11 (91.7%)	
Occupation n (%)			
Employed	4 (33.3%)	2 (16.7%)	0.64
Unemployed	8 (66.7%)	10 (83.3%)	
Smoking n (%)			
Yes	3 (25.0%)	1 (8.3%)	0.59
No	9 (75.0%)	11 (91.7)	
Alcohol n (%)			
Yes	1 (8.3%)	-	1.00
No	11 (91.7%)	12 (100%)	
ESR (mm/h)*	61.2±26.8	51.5±24.3	0.36
CRP (mg/L)**	33,8 [21.5-39.1]	14,8 [4.4-30.1]	**0.01**
Anxiety Status***			
Mild	7 (58.3%)	5 (41.7%)	
Moderate to severe	3 (25.0%)	-	**0.02**
Severe	1 (8.3%)	-	
Hamilton Anxiety Rating Scale Score**			
Psychological	6.0 [4.2-8.0]	3.0 [1.2-5.0]	**0.02**
Somatic	8.0 [6.0-10.7]	3.5 [2.2-5.0]	**0.07**
Spielberger State-Trait Anxiety Inventory Score*			
State Anxiety	47.4±6.8	40.5±6.5	**0.01**
Trait Anxiety	52.0±5.6	34.9±6.0	**<0.001**

*mean± standard deviation; **median [25-75p]; ***Hamilton Anxiety Rating Scale n (%); ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

A significant correlation was found between CRP and overall score, sleep quality, with the correlation coefficient 0.429 and 0.111, respectively (p<0.05). The sleep latency, efficiency, duration, disturbance, medication, daytime dysfunction, and sleep quality were found to be correlated with Hamilton Anxiety Rating Scale Score, STAI-S, and STAI-T score. There was no significant correlation between STAI-T and sleep medication. Correlation coefficients between components of PSQI and clinical, laboratory, and anxiety scores in patients with TA are presented in Table 4.

Table 4. Correlation coefficients between components of Pittsburgh sleep quality index and clinical, laboratory and the anxiety scores in patients with Takayasu Arteritis

	Overall score	Sleep Latency	Sleep efficiency	Sleep duration	Sleep disturbance	Sleep medication	Daytime dysfunction	Sleep quality
Age (years)	0.079	0.028	0.183	0.085	0.009	0.220	0.078	0.211
Disease duration (months)	-0.233	-0.358	-0.044	-0.062	-0.107	-0.127	-0.168	-0.017
ESR (mm/h)	0.306	0.417	0.192	0.370	0.386	0.257	0.025	0.184
CRP (mg/L)	0.429*	0.273	0.214	0.183	0.170	0.270	0.111	0.440*
Hamilton Anxiety Rating Scale Score Psychological Somatic	0.652** 0.700**	0.516** 0.558**	0.404* 0.410*	0.635** 0.451*	0.566** 0.523**	0.474* 0.457*	0.438* 0.577**	0.415* 0.552**
Spielberger State-Trait Anxiety Inventory Score State Anxiety Trait Anxiety	0.667** 0.822**	0.583** 0.761**	0.560** 0.671**	0.521** 0.500*	0.484* 0.452*	0.407* 0.286	0.476* 0.663**	0.455* 0.528**

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; *p < 0.05; **p < 0.01

4. Discussion

In the present study, sleep quality and anxiety were investigated in patients with TA. In our results, we observed a correlation between anxiety scores and PSQI. ESR values were not different between the good sleeper and poor sleeper Takayasu patients. There was a correlation between CRP and overall and sleep quality scores of the PSQI, while a similar was not found for ESR. The presence of systemic symptoms was associated with poor sleep. Moreover, the anxiety scores were higher in poor sleepers compared to the good sleepers in TA patients.

Elevated acute phase reactants such as ESR and CRP indicate inflammation and active disease in TA. Although ESR and CRP are neither highly sensitive nor specific for disease activity in TA, they are still used in clinical practice to monitor disease activity and incorporated into the NIH disease activity score as well as the Indian Takayasu Clinical Activity Score disease activity measurement (18). The progressive inflammatory pattern and active disease have been reported to be associated with poor outcomes and postoperative complications in TA (19). Inflammation, increase in the permeability of the blood-brain barrier, structural and functional changes in the central nervous system play an important role in the development of depression and fatigue (7). The association between rheumatic disease activity with depressive symptoms and fatigue was found in chronic rheumatologic diseases (20). Improvement in fatigue by blocking inflammatory cytokines with biological agents supports this. (20).

In TA, the mood, happiness, energy levels, and thus daily life activities of the patients are affected (21). In fact, it was reported that there were changes in their working life and their job duties and they resigned from their jobs (21). In addition, quality of life is associated with disease activity and better quality of life with disease remission in TA (21). Nevertheless, chronic inflammation and disease activity have less effect on fatigue in TA than inflammatory diseases such as RA and SLE (22). Even so, supportive help is required in these areas due to the association of disease activity with anxiety and depression (13). In our study, we found the correlation of CRP with STAI-T (p=0.04, r=0.406), and ESR with psychological anxiety score (p=0.006, r=0.540) in TA. Also, ESR (63.6±26.6 vs 42.0±16.1; p=0.03) and CRP (31 vs 21.3; p=0.21) were high in TA with anxiety compared to TA without anxiety. Moreover, there was a significant difference for systemic symptoms in anxiety patients compared to the non-anxiety group (p=0.02).

In a study, it was reported that anxiety and depression were higher in TA compared to healthy controls (13). Similarly, our patients had higher anxiety scores than healthy controls. We found the median psychological anxiety score to be 5.0 and the somatic anxiety score to 5.5. In addition, the evaluations of the data obtained from STAI-S and STAI-T were similar to Hamilton Anxiety Rating Scale. It has been observed that both anxiety and depression are associated with the Study 36-Item Short-Form (SF-36) parameters in TA (13). Also; anxiety appears to be a permanent feature of mental health, due to the long-term consequences that impair the mental state.

Sleep is essential for learning, memory, and cognitive functions. So, sleep disorders and insufficient sleep may lead to many problems such as impaired quality of life, anxiety, depression, and poor physical status to death risk (23,24). Various studies have reported sleep disorders and poor sleep quality in ankylosing spondylitis, primary Sjogren's syndrome, Behçet's disease (BD), and RA (23-26). To our knowledge, there is no data on this issue in patients with TA. The studies mainly focused on comparing the sleep quality of BD patients with healthy volunteers (27-29). In overview59.8% of all BD patients have been reported to have

sleep problems (26). Higher scores for subjective sleep quality, sleep efficiency, sleep delay, and more sleep disturbance had been found in BD than healthy controls (27,28). In our study; sleep efficienty, sleep disturbance, daytime dysfunction, subjective sleep quality, and overall score were significantly higher in TA compared to healthy control. Lee et al. reported a positive correlation between disease activity and PSQI parameters such as subjective sleep quality, sleep duration, and sleep latency in patients with BD (29). When evaluated in terms of disease activity in our study, ESR and CRP levels were higher in patients with a diagnosis of TA compared to healthy controls and good sleepers. Moreover, there was a significant difference for CRP and the presence of systemic findings, but not for ESR were found between poor and good sleepers in TA. The study has a few limitations. Although the sample size is relatively small in our study, it is generally difficult to have a large number of samples in TA due to its rare presence. TA is a very rare disease and the number of cases was here in the single center. The sleep disturbance was only evaluated by a self-reported questionnaire and disease activity was only assessed with ESR and CRP. And, the information about the long-term results of the study is not known. To our knowledge, there have been no previous studies regarding sleep quality and its association with anxiety in patients with TA.

In conclusion, the present study has demonstrated higher anxiety scores and poor sleep quality among patients in TA compared with healthy controls. It seems that many PSQI parameters have significantly impaired in TA. Poor sleepers had higher disease activity, especially higher CRP, and also more anxiety. In particular, TA patients with systemic findings and high inflammation should be evaluated for poor sleep quality. Also, remission in disease activity may be associated with better sleep and less anxiety scores.

Conflict of interest

None to declare.

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None to declare.

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