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The relationship of depression with fatigue, quality of life, and gastrointestinal symptoms in patients with restless legs syndrome

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ABSTRACT

Aims: This study examined the relationship between depression with fatigue, quality of life (QoL), and gastrointestinal symptoms in patients with restless legs syndrome (RLS).

Methods: This prospective study included patients diagnosed with RLS. Depression, fatigue, QoL and gastrointestinal symptoms were evaluated with Hospital Anxiety and Depression Scale, the Fatigue Severity Scale, RLS QoL Questionnaire and Gastrointestinal Symptom Rating Scale, respectively. Multiple regression was performed to determine the relationship between fatigue, QoL, gastrointestinal symptoms, and depression.

Results: The final sample included 19 patients [mean age: 42.6±12.7 years, female: 11 (57.9%)]. The level of depression positively correlated with fatigue, QoL, and gastrointestinal symptoms scores. These variables explained 57.1% of the variance in depression scores in patients with RLS ($R=0.755$, $R^2=0.571$ $F=6.645$; $p=0.005$).

Conclusions: This study showed that patients with RLS experience worsening QoL, fatigue, and increased gastrointestinal symptoms with increasing depression scores. Managing RLS may require tackling depression and depression-related symptoms with a multifaceted approach.

Introduction

Restless legs syndrome (RLS) is a neurological sensorimotor disorder diagnosed by four main criteria (unintentional need to move the legs, typically accompanied by unpleasant leg sensations; induction or exacerbation of symptoms while at rest; symptom relief while activity; and daily fluctuations with symptoms getting worse in the evening and at night) (1). The most common symptoms of RLS are sleep disturbances such as reduced sleep duration, periodic extremity movements, and changes in sleep architecture (2).

Depression and anxiety, which often negatively affect sleep, are common in patients with RLS. Generally, many functions of patients with RLS patients are restricted, and these patients have a higher level of somatic stress and worsened sleep (3). It has also been suggested that RLS patients have a lower quality of life (QoL) than patients with other chronic medical conditions such as high blood pressure, congestive heart failure, and diabetes mellitus (4). The impact of RLS on mental health has been well recognized and the diagnostic criteria for RLS are included in the Diagnostic and Statistical Manual of Mental Disorders-V (5).

Studies have shown that people with RLS have a 2- to 4-fold increased risk of developing a depressive illness. The high frequency of depression in RLS suggests a link between the two conditions (6,7). Moreover, the severity of RLS correlates with the symptoms of depression and anxiety (8). Finally, comorbid

depression may substantially impact overall treatment success (7). On the other hand, some antidepressant drugs can trigger or worsen symptoms and periodic limb movements in RLS (9). Cuellar et al. (10) investigated the effect of depression on sleep quality, sleepiness, and fatigue in patients with RLS, some of whom were receiving RLS therapy and antidepressant medications. They showed that depressed patients with RLS had worse sleep quality and fatigue, but their sleepiness was not affected by depression. Additionally, although the association between QoL and depression has been previously investigated, the relationship between RLS-specific QoL and depression is still unknown.

The World Health Organization defines health as a condition of whole (physical, mental, and social) well-being and not only the absence of sickness or infirmity (11). Because health has many components, it is not effective enough to treat symptoms alone in patients with RLS. Thus, a holistic approach that includes mental and social health components such as fatigue, depression, and QoL is needed. Additionally, the importance of gastrointestinal symptoms, which have dramatic adverse effects on patients' QoL has increased rapidly. However, there are limited studies on gastrointestinal symptoms in patients with RLS. Determining the relationship between depression, which is common in RLS (6,7), and QoL, gastrointestinal symptoms, and fatigue may help improve the management of the disease. Therefore, this study examined the relationship between depression with fatigue, QoL, and in patients with RLS.

Methods

Study design and participants

We prospectively enrolled patients with RLS admitted to the Department of Movement Disorders of the Neurology Outpatient Clinic, Gülhane Training and Research Hospital, at the University of Health Sciences Türkiye, between September 2021 and March 2022. The ethics board of the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (protocol number: 2020-422, date: 17.12.2020) approved the study protocol. The procedures were conducted in accordance with the Declaration of Helsinki. All participants were informed about the protocol and gave written consent.

The inclusion criteria were (1) diagnosis of RLS by the neurologist according to the International RLS Study Group 2014 criteria (12), (2) age over 18 years, and (3) being literate. The exclusion criteria were (1) the presence of other sleep disorders, (2) gastrointestinal system diseases, (3) the use of antipsychotics, psychoactive, and antidepressant drugs, and (4) scores <24 on the Mini-Mental State Examination (13).

Outcome measures

The same researcher performed the procedures. Standardized questionnaires were used to collect demographic and physical characteristics and medical history. All the questionnaires were self-reported. The Mini-Mental State Examination was used to determine the cognitive status of the patients (13).

Depression

The Hospital Anxiety and Depression Scale (HADS) was used as a self-assessment tool to determine the state of depression (14,15). It has two domains that determine the level of anxiety (HADS-A) and depression (HADS-D) and consists of 14 items, of which odd-numbered items investigate anxiety (HADS-A) and even-numbered items investigate depression (HADS-D). Each item is scored between 0 and 3, and the total score ranges between 0 and 21 for each domain. Higher scores indicate more severe depression. We used only HADS-D in the current study.

Fatigue

We evaluated fatigue using the "Fatigue Severity Scale (FSS)" (16,17), which consists of 9 sub-items related to fatigue-related daily activities. Each item is scored between 0 and 7 and the total score is the sum of arithmetic means. A total score of 4 or higher indicates severe fatigue.

Quality of life

The RLS QoL Questionnaire (RLS-QoL) was used to evaluate the QoL (18,19). It consists of 18 items, and items 1-5-7-10 and 13 are scored between 1 and 5. The total score is calculated using the formula:

[(Actual raw score - lowest possible raw score) / Possible raw score range] × 100.

Higher scores indicate worse QoL.

Gastrointestinal symptoms

The Gastrointestinal Symptom Rating Scale (GSRS) was used to determine common gastrointestinal symptoms, which consisted of 15 items and five subdimensions: abdominal pain (items 1, 4, and 5), reflux (items 2 and 3), indigestion (items 6, 7, 8, and 9), diarrhea (items 11, 12, and 14), and constipation (items 10, 13, and 15) (20,21). Each item is scored between 0 (no symptom) and 7 (severe discomfort) on a Likert scale and calculated as the mean score. Higher scores indicate more severe symptoms.

Statistical Analysis

The Statistical Package for the Social Sciences version 25.0 (IBM Corporation, Armonk, NY, United States) was used for analysis. Data were expressed as mean±standard deviation, medians (minimum maximum), and percentages. Data normality was checked by normal probability plots, the Shapiro-Wilk test, and coefficients of skewness and kurtosis.

Pearson correlation was used to assess the linear relationships between continuous variables. Multiple regression was used to estimate the relationship between fatigue, QoL, gastrointestinal symptoms, and depression scores. Regression analysis was performed using the depression score as the dependent variable and fatigue, QoL, and gastrointestinal symptoms as independent variables. Analysis of variance (ANOVA) was used to check the validity of the regression model. Correlation levels were rated: <0.20: poor; 0.20-0.39: fair; 0.40-0.69: moderate; 0.70-0.89: excellent; >0.90: excellent. The significance level was set at α=0.05 (22).

Results

We evaluated 27 patients for eligibility. Three participants with non-RLS sleep disorders, 4 patients who were on antipsychotics, psychoactive, or antidepressant medications, and 1 patient with cognitive problems were excluded. The study was completed with 19 patients. The mean age was 42.6±12.7 years and 57.9% of the participants were women. The mean body mass index was 27.3±4.9. Table 1 shows the characteristics of the patients. No patient reported alcohol intake and 15.8% (n=3) reported smoking. Family history of RLS was recorded by 47.4% (n=9). The disease duration varied between 2 months and 17 years.

Of the patients, 36.8% showed depression symptoms. Four of the depressed patients were women and 3 were men. The mean±SD age of patients with RLS with depression was 37.1±11.7 years, while the mean±SD age of non-depressed patients was 45.9±12.5 years. The FSS score of the patients was 4.9±1.6 and 3.1±0.9 in depressed and non-depressed patients, respectively. The RLS-QoL score of patients with depression and without depression was 66.7±19 and 37.9±19.6, respectively. The GSRS score was 12.0±4.13 and 8.6±3.5 in depressed and non-depressed patients, respectively.

HADS-D scores positively correlated with FSS, RLS-QoL and GSRS (r=0.66, p=0.001; r=0.49, p=0.015 and r=0.39, p=0.049, respectively). Multiple linear regression was performed to predict the HADS-D score based on fatigue, QoL, and gastrointestinal symptoms. A significant regression equation was found [F (3,15)=6.645, p=0.005, with an R2 of 0.571]. Participants predicted HADS-D score is equal to -2.920 (constant) + 1.195 (fatigue score) + 0.051 (QoL score) + 0.320 (gastrointestinal symptoms score), where fatigue, QoL, and gastrointestinal symptoms were assessed as scale variables. The results of multiple regression analyzes are shown in Table 2. The variance inflation factor of a maximum of 1.5 indicates the absence of multicollinearity in the regression model. There was no heteroscedasticity in the final model.

Table 1. Basic characteristics of patients

Characteristics	Patients (n=19)
Gender, n (%)	
Female	11 (57.9)
Male	8 (42.1)
Age, year, mean±SD	42.6±12.7
BMI, kg/m², mean±SD	27.3±4.9
Marital status, n (%)	
Married	14 (73.7)
Single	5 (26.3)
Education, n (%)	
Primary school	3 (15.8)
Middle school	2 (10.5)
High school	5 (26.3)
College	7 (36.8)
Master's degree	2 (10.5)
Smoking, n (%)	
Yes	3 (15.8)
No	16 (84.2)
Family history of RLS, n (%)	
Yes	9 (47.4)
No	10 (52.6)
Occupation, n (%)	
Unemployed	5 (26.2)
Retired	2 (10.5)
Blue-collar worker	5 (26.3)
Student	3 (15.8)
White-collar worker	4 (21.1)
Alcohol use, n (%)	
Yes	**0 (0)**
No	**19 (100)**
Medication use, n (%)	
Yes	12 (63.2)
No	7 (36.8)
Medical history, n (%)	
None	12 (56.4)
Varicose veins	2 (9.5)
Hashimoto's thyroiditis	2 (9.5)
Familial Mediterranean fever	1 (4.7)
Arrhythmia	1 (4.7)
Diabetes mellitus	1 (4.7)
Hypertension	1 (4.7)
Thyroid nodule	1 (4.7)
Disease duration, [month, median (min-max)]	48 (2-204)
Hospital Anxiety and Depression Scale, mean±SD	7.2±4.0
Fatigue Severity Scale, mean±SD	3.7±1.4
RLS Quality of Life, mean±SD	48.5±23.9
Gastrointestinal Symptom Rating Scale mean±SD	9.8±4.0

SD: Standard deviation, BMI: Body mass index, RLS: Restless legs syndrome, min-max: Minimum-maximum

Table 2. Results of the analysis of variance (ANOVA) and multiple regression

	Unstandardized coefficient (t)		Standardized coefficient	95% confidence interval for B		p	VIF
	B	S	Beta (t)	Lower bound	Upper bound		
Constant	-2.920	2.467	-	-8.179	2.339	0.255	-
Fatigue	1.195	0.563	0.441	-0.004	2.394	0.051	1.503
Quality of life	0.051	0.034	0.304	-0.022	0.125	0.155	1.437
Gastrointestinal symptoms	0.320	0.180	0.318	-0.064	0.704	0.096	1.123

n=19, R=0.755, R^2=0.571, Adj. R^2=0.485, (F=6.645; p=0.005).
SD: Standard deviation, VIF: Variance inflation factor

Discussion

The current study found strong associations between the levels of depression and fatigue, QoL, and gastrointestinal symptoms. These variables explained about 60% of the depression level in patients with RLS. Demographic findings were in line with the literature, with examples of RLS being more common in women, frequent familial history, and the presence of different comorbidities (3,23,24).

The findings of the study demonstrated a relationship between fatigue and depression in patients with RLS patients. Similarly, the study by Cuellar et al. (10) showed more exhaustion among depressed patients with RLS. The authors also investigated sleepiness and sleep quality among depressed patients with RLS taking or not taking antidepressants and observed that while the sleep quality of depressed people deteriorated sleeplessness was not altered. Our study differs from that study in that we excluded patients taking antidepressants because medications can alter the level of depression and gastrointestinal symptoms. Evidence indicating inflammation plays a role in the development of various forms of depression and fatigue includes the connection between fatigue, depression, and immunological activity, the psychological effects of proinflammatory insults, and the effectiveness of anti-inflammatory medications as therapy (25). The finding of the current study suggests that depression, besides sleep difficulties, contributes to the fatigue experienced by patients with RLS.

RLS causes a unique burden on both the physical and mental dimensions of patients' QoL (26). The decrease in QoL appears more significant than other common chronic diseases (4). This study evaluated QoL in terms of RLS rather than a general perspective. For this reason, we applied an RLS-specific QoL measurement scale. QoL is a multifaceted concept that can be affected by different conditions. Revealing the relationship between depression and QoL may show the importance of approaching RLS such as fibromyalgia, which also has a higher prevalence in these patients, within a biopsychological model (27).

The link between psychological problems and gastrointestinal symptoms is often explained by the brain-gut axis, which refers to the rich bidirectional molecular interaction between the gastrointestinal tract and the central nervous system (28). People who do not have high levels of anxiety and depression at baseline feel significantly depressed and anxious during the follow-up period in the presence of functional gastrointestinal diseases, including functional dyspepsia (29). Simultaneously, higher levels of depression predict functional dyspepsia (29). Chronic diarrhea and constipation have also been common among depressed patients (30). Furthermore, even in the absence of severe gastrointestinal diseases, abdominal pain is linked to depression symptoms (31). Finally, indigestion can cause depression (32). RLS is prevalent in patients with irritable bowel syndrome, which presents in the form of diarrhea predominance, constipation predominance, or both (33). Dyspepsia incidence is eight times higher in patients with irritable bowel syndrome (34). Therefore, our findings of increased gastrointestinal symptoms along with depression symptoms are in line with the previous studies (30,31).

Study Limitations

The major strength of this study is its focus on the relationship between depression and fatigue, QoL, and gastrointestinal symptoms in patients with RLS who were not on antidepressant treatment. One major limitation of the study is the small sample size caused by the single-center study design, exclusion of antidepressant users, and difficulties in patient enrollment during the Coronavirus disease-2019 pandemic. The other major limitation is the lack of a control group.

Conclusion

In conclusion, this study determined that as the level of depression increases, the QoL decreases, and the complaints of fatigue and gastrointestinal symptoms increase in patients with RLS. Treatment of depression may be effective in reducing the associated fatigue and gastrointestinal symptoms and improving the QoL.

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Ethics

Ethics Committee Approval: The ethics board of the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (protocol number: 2020-422, date: 17.12.2020) approved the study protocol.

Informed Consent: All participants were informed about the research, and written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.R.S., Concept: Ö.Ç., M.E.Y., A.R.S., N.Ü.Y., Design: Ö.Ç., M.E.Y., A.R.S., N.Ü.Y., Data Collection or Processing: Ö.Ç., Analysis or Interpretation: Ö.Ç., Literature Search: Ö.Ç., Writing: Ö.Ç., M.E.Y., A.R.S., N.Ü.Y.

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