Original Article

Sleep-related Quality of Life in Patients with Myasthenia Gravis

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Aim: Myasthenia gravis (MG) is an autoimmune neuromuscular junction disease. Sleep quality and quality of life are often affected by MG. This study aimed to evaluate the impact of sleep quality on the quality of life in patients with MG, along with other associated factors. **Materials and Methods:** A total of 81 patients with MG were recruited. The Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, Beck Depression Inventory (BDI), Fatigue Severity Scale (FSS), and MG-specific 15-item quality of life scale (MG-QoL15) were administered to the patients. The results were statistically compared. **Results:** In the 81 patients with MG, the median duration of disease was 36 (range, 1–264) months. The mean PSQI score was 5.83 ± 3.51. A significant relationship was found between sleep quality and quality of life, depression, fatigue, and body mass index. Positive correlations were observed between MG-QoL15, BDI, and FSS scores. Female sex, the presence of depression, and obesity were found to be effective in predicting poor sleep quality. **Discussion and Conclusion:** In this cross-sectional study, we explored the potential relationships between sleep quality, depression, fatigue, and quality of life. Approximately 50% of the study participants experienced poor sleep quality. A significant relationship was found between poor sleep quality and the presence of depression, fatigue, and poor quality of life. Excessive daytime sleepiness was seldom observed. In conclusion, the presence of depression, female sex, and obesity are determinant factors in predicting poor sleep quality in MG.

Keywords: *Depression, fatigue, myasthenia gravis, quality of life, sex, sleep quality*

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Introduction

Myasthenia gravis (MG), the most common neuromuscular junction disorder, is a chronic autoimmune disease characterized by fluctuating muscle weakness and fatigue that varies throughout the day. Antibodies against postsynaptic acetylcholine receptors located at the motor endplate play a role in the autoimmune pathogenesis of the disease. Weakness increases with the use of muscles and ameliorates with rest. The treatment of MG includes the use of acetylcholinesterase inhibitors, corticosteroids, and immunosuppressive drugs. Currently, there is no cure for MG, and treatment focuses on managing symptoms.[1]

The chronic course of MG, with its exacerbations and remissions, typically exerts a negative impact on the quality of life for affected patients. There is extensive research on the quality of life (QoL) of patients with MG.[2-8] In most of these studies, a negative correlation between QoL and disease severity has been observed.[2-4,7,8] However, research regarding sleep-related disorders in patients with MG and their relationship with sleep quality remains limited. The distribution of muscle weakness, including the bulbar and respiratory muscles, suggests that it can significantly impact the quality of life and sleep by causing respiratory disturbances. An increased incidence of sleep-disordered breathing and obstructive sleep apnea has been observed in patients with MG.[9,10] Patients with well-controlled MG may have abnormal breathing during sleep without any daytime

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muscle dysfunction.[10] Some studies have also noted that excessive daytime sleepiness is not prevalent in patients with MG.[11,12] There has been a reported association between corticosteroid use and the risk of sleep disorders.[12] In addition to common factors associated with sleep disturbances (e.g. age, male sex, and obesity), MG-specific factors can contribute to sleep disorders. In particular, the lack of clinical stability should be considered a risk factor for poor sleep quality.[13]

It has been found that the MG-QoL15 correlates with the Pittsburgh Sleep Quality Index (PSQI) in clinically stable patients with MG.[13] The MG-QoL15, a specific 15-item quality-of-life questionnaire for patients with MG, can be used to assess quality of life. In addition, the PSQI and Epworth Sleepiness Scale (ESS) can be used to assess sleep quality. Evaluating sleep and quality of life in MG can help to identify factors affecting a patient well-being and improve adherence to the treatment. By addressing these factors, the QoL and productivity of patients with MG may potentially improve. Furthermore, it can contribute to solving issues such as unnecessary medication use or changes in treatment modalities, thereby improving patient management.

In this study, our aim was to assess sleep and quality of life in patients with MG and to examine the relationship between clinical parameters.

Materials and Methods

Eighty-one consecutive patients with MG who were followed at our neuromuscular disease clinic were enrolled in the study from February 2017 to August 2017. This cross-sectional and analytical study was conducted as a single-center study. Ethical approval was obtained from the Clinical Research Ethics Committee on January 25, 2017 (decision number 1). Throughout the study, we carefully followed the principles of the Helsinki Declaration. Written informed consent was obtained from all patients before they participated in the study.

The inclusion criteria were patients with definite MG, either ocular or generalized, aged 18 years or older, who had sufficient cognitive abilities to complete the clinical assessment forms. The exclusion criteria were being clinically unstable, having insufficient cognitive capacity to complete the questionnaires, and having a previous diagnosis of a sleep disorder. Demographic characteristics (sex, age, height, body weight, and body mass index (BMI)), the presence of comorbid chronic diseases (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, thyroid diseases, atrial fibrillation, osteoporosis, depressive disorder, anxiety disorder, and bipolar disorder), and clinical parameters (clinical classification, disease severity, anti-AChR antibody positivity, previous thymectomy, and medications used) were recorded.

Clinical assessment scales

The clinical assessment involved face-to-face interviews, during which the following scales were administered: PSQI,[14,15] ESS,[16,17] MG-QoL15,[6,18,19] the Beck Depression Inventory (BDI),[20,21] and the Fatigue Severity Scale (FSS).[22,23]

Poor subjective sleep quality was present at a PSQI score of 5 or higher (range 0–21). In the ESS, a total score higher than 10 (range, 0–24) is considered excessive daytime sleepiness. The MG-QoL15 questionnaire has a score range of 0–60, with a higher total score indicating lower quality of life in patients with MG. In our study, patients with a BDI score (range, 0–64) of 11 or higher were considered having depression. Fatigue was considered present at an FSS score of 4 or higher (range, 0–7). The patients were grouped according to the World Health Organization's BMI classification.[24] The 2000 version of the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification was used to determine the clinical features.[25,26] According to this classification, Class 1 represents only ocular weakness; Class 2 represents mild generalized weakness, with or without ocular involvement; Class 3 represents moderate generalized weakness, with or without ocular involvement; Class 4 represents severe generalized weakness, with or without ocular involvement; and Class 5 indicates requirement for intubation.

Statistical analysis

Statistical analysis of the collected data was performed using the SPSS 24.0 software (IBM Corporation, Armonk, New York, United States). The normal distribution of data was assessed using the Shapiro–Wilk test, and the homogeneity of variances was examined using the Levene test. When comparing independent groups based on quantitative data, the independent-sample *t*-test was used, along with Bootstrap results. The Mann–Whitney *U* test, along with Monte Carlo results, was employed when necessary. Kendall's tau-b test was used to investigate correlations between variables. For the comparison of categorical variables, the Pearson's Chi-square, Fisher's exact, and Fisher–Freeman–Holton tests were used, along with exact and Monte Carlo results. Odds ratios were used to indicate how many times greater the risk factor was for those with it compared to those without it. Logistic regression analysis using the Backward method was performed to determine cause-and-effect relationships between binary categories of the categorical response variable and

explanatory variables. Sensitivity and specificity, which assess the relationship between the classification based on the cutoff values calculated for the groups concerning the variables and the actual classification, were examined and expressed through receiver operating characteristic curve analysis. Quantitative variables are presented as means ± standard deviation and medians with ranges (maximum-minimum), and categorical variables are expressed as *n* (%). A 95% confidence interval (CI) level was adopted for the analysis, with $P < 0.05$ indicating statistical significance.

Results

A total of 81 patients were included in this study, with ages ranging from 18 to 86 years. Of these, 45 (55.56%) were female, and 36 (44.44%) were male. The mean age of the patients was 55.36 ± 16.10 years. BMI values ranged from 18.50 to 43.34 kg/m², with a mean of 27.97 ± 5.07 kg/m². The BMI distribution among the patients showed that 24 (29.63%) had normal BMI, 35 (43.21%) were overweight, and 22 (27.2%) were obese [Table 1].

According to the MGFA clinical classification, 30 patients (37.04%) were in Class 1 (only ocular weakness), 23 (28.40%) in Class 2a (predominantly affecting limb or axial muscles, or both, and possibly involving oropharyngeal muscles to a lesser extent), 24 (29.63%) in Class 2b (predominantly affecting oropharyngeal or respiratory muscles, or both, with lesser or equal involvement of limb or axial muscles, or both), and 4 (4.94%) in Class 3b (predominantly affecting oropharyngeal or respiratory muscles, or both, with lesser or equal involvement of limb or axial muscles, or both). Seventeen patients (20.98%) had serum antibody tests, and 11 were positive for anti-AChR antibodies. The remaining 64 patients met the diagnostic criteria for MG without undergoing antibody testing. Because the primary aim of our study was not to interpret or compare results based on antibody testing, we did not deem it necessary to test all patients. The median disease duration was 36 (range, 1–264) months. Thirty-seven patients (45.68%) had no comorbidities, 22 (27.16%) had one comorbidity, and 22 (27.16%) had two or more comorbidities [Table 1]. Regarding medications for MG, 10 (12.35%) patients did not use any MG-specific medication, 12 (14.81%) received symptomatic treatment (pyridostigmine) only, 28 (34.57%) used immunosuppressant medications (steroids and/or azathioprine) alone, and 28 (34.57%) received both immunosuppressant and symptomatic treatments. In addition, three (3.70%) patients received regular high-dose intravenous immunoglobulin treatment in addition to symptomatic and immunosuppressant therapy [Table 2]. Thymectomy was performed in 14 (17.28%) patients [Table 2]. Sixteen patients (19.75%) were using antidepressant

Table 1: Baseline data according to sleep quality (Pittsburgh sleep quality index score)

	Pittsburg Sleep Quality Scale			χ^2	*P*
	Normal, *n* (%)	Abnormal, *n* (%)	Total, *n* (%)		
Age (years)	55±17.03	55.76±15.20	55.36±16.10		0.844
Sex					
Female	17 (39.53)	**28 (73.68)**	45 (55.56)	9.528	**0.003**
Male	26 (60.47)	10 (26.32)	36 (44.44)		**4.35 (1.67–11.11)***
Comorbidity status					
None	24 (55.81)	13 (34.21)	37 (45.68)	3.794	0.074
Present	19 (44.19)	25 (65.79)	44 (54.32)		
Antidepressant use					
None	35 (81.40)	30 (78.95)	65 (80.25)	0.076	0.999
Present	8 (18.60)	8 (21.05)	16 (19.75)		
BMI (kg/m^2)					
Normal	14 (32.56)	10 (26.32)	24 (29.63)	14.016	0.003
Overweight	24 (55.81)[b]	11 (28.95)	35 (43.21)		
Obesity Class 1	2 (4.65)	13 (34.21)[a]	15 (18.52)		
Obesity Class 2	2 (4.65)	3 (7.89)	5 (6.17)		
Obesity Class 3	1 (2.33)	1 (2.63)	2 (2.47)		
BMI					
Normal	38 (88.4)	21 (55.3)	59 (72.8)	11.178	**0.001**
Obese	5 (11.6)	17 (44.7)	22 (27.2)		615 (1.98–19.06)*

*OR (95% CI) phi: Correlation coefficient, [a]Significant compared with the normal group, [b]Significant compared with the pathologic group. Those with $P<0.05$ were considered statistically significant. Significant *P* values are indicated in bold. Mean 6 (SD) unless otherwise stated. SD: Standard deviation, BMI: Body mass index, CI: Confidence interval, OR: Odd ratio

Table 2: Clinical parameters: correlation with Pittsburgh sleep quality index scores

	Pittsburg Sleep Quality Scale			χ^2	*P*
	Normal, *n* (%)	Abnormal, *n* (%)	Total, *n* (%)		
Medication use for MG					
None	6 (13.95)	4 (10.53)	10 (12.35)	0.219	0.743
Present	37 (86.05)	34 (89.47)	71 (87.65)		
Medication group used for MG					
Absent	6 (13.95)	4 (10.53)	10 (12.35)	1.299	0.887
Only IS	16 (37.21)	12 (31.58)	28 (34.57)		
IS + symptomatic	13 (30.23)	15 (39.47)	28 (34.57)		
Symptomatic	6 (13.95)	6 (15.79)	12 (14.81)		
Monthly IVIg + IS/symptomatic	2 (4.65)	1 (2.63)	3 (3.70)		
MGFA clinical classification					
Class 1	16 (37.21)	14 (36.84)	30 (37.04)	1.359	0.775
Class 2a	13 (30.23)	10 (26.32)	23 (28.40)		
Class 2b	11 (25.58)	13 (34.21)	24 (29.63)		
Class 3b	3 (6.98)	1 (2.63)	4 (4.94)		
Serum anti-AChR antibody					
Positive	6 (66.67)	5 (62.50)	11 (64.71)	0.032	0.999
Negative	3 (33.33)	3 (37.50)	6 (35.29)		
Thymectomy					
None	34 (79.07)	33 (86.84)	67 (82.72)	0.852	0.394
Present	9 (20.93)	5 (13.16)	14 (17.28)		
Disease duration (months), median (minimum–maximum)	36 (1–262)	36 (1–264)	36 (1–264)		0.812

MG: Myasthenia gravis, IS: Immunosuppressive, MGFA: MG Foundation of America, AChR: Acetylcholine receptor, IVIg: Intravenous immunoglobulin

medications. Based on the BDI scores, 50 (61.7%) patients did not exhibit symptoms of depression.

According to the PSQI scores, 38 (46.91%) patients had poor sleep quality. Based on ESS scores, 12 (14.81%) patients experienced excessive daytime sleepiness. Fatigue was observed in 36 (44.44%) patients based on FSS scores [Table 1]. When patients were divided into two groups, those with good or poor sleep quality based on the PSQI assessment, statistically significant differences were observed between the two groups in terms of MG-QoL 15 values, BDI scores, and FSS scores ($P = 0.043$, $P < 0.001$, and $P < 0.001$, respectively) [Table 3], and no statistically significant difference was found in terms of age, disease duration, and excessive daytime sleepiness ($P = 0.844$, $P = 0.812$, and $P = 0.509$, respectively) [Tables 1-3]. Thirty-six (72%) of 50 patients who were not depressed, according to the BDI score, had good sleep quality. At the same time, 24 (77.4%) of 31 patients with symptoms of depression had poor sleep quality.

The sleep quality in females was significantly worse compared with males ($P = 0.003$). Being female was found to increase the likelihood of having poor sleep quality by 4.3 times (95% CI: 1.67–11.11) [Table 1]. A statistically significant relationship was observed between PSQI scores and BMI ($P = 0.001$). In patients with poor sleep quality, Class 1 obesity was significantly more prevalent (34.21%), and in the group with good sleep quality, overweight patients constituted a higher proportion (55.81%) [Table 1].

Table 3: Comparison of patients according to sleep quality in terms of quality of life, fatigue, depression, and Epworth Sleepiness Scale

	Pittsburg Sleep Quality Scale			*P*
	Normal, median (minimum–maximum)	Abnormal, median (minimum–maximum)	Total	
MG-QOL15	8 (0–55)	15 (1–51)	11 (0–55)	**0.043**
BDI	4 (0–32)	10.50 (2–52)	7 (0–52)	**<0.001**
FSS	3 (0–7)	5 (1–7)	4 (0–7)	**<0.001**
ESS	6 (0–21)	4 (0–17)	6 (0–21)	0.509

Significant *P* values are indicated in bold. MG-QoL15: Myasthenia Gravis Quality of Life Scale, BDI: Beck depression inventory, FSS: Fatigue Severity Scale, ESS: Epworth Sleepiness Scale

A positive and low significant correlation was found between PSQI scores and MG-QoL15 scores ($r = 0.271$, $P = 0.001$). In addition, a positive and moderately significant correlation between PSQI scores and both BDI and FSS scores ($r = 0.420$, $P < 0.001$; $r = 0.326$, $P < 0.001$, respectively). As PSQI scores increased, quality of life scores, BDI, and FSS scores also increased. Correlations were found between poor sleep quality and low quality of life, the presence of depression, and the

severity of fatigue [Table 4]. MG-QoL15 scores had a positive and moderately significant correlation with BDI and FSS scores (r = 0.430, P < 0.001; r = 0.480, P < 0.001, respectively). As MG-QoL15 scores increased, BDI and FSS scores also increased. Correlations were found between poor quality of life, the presence of depression, and the severity of fatigue [Table 4].

Statistically significant variables associated with PSQI were included in the model, and logistic regression analysis was performed using a backward elimination method. The logistic regression analysis identified BDI, sex, and BMI as significant predictors of poor sleep quality (P = 0.001, 0.049, and 0.028, respectively) [Table 5]. Specifically, a high BDI score increased the likelihood of poor sleep quality by 6.5 times, being female increased the likelihood of poor sleep quality by 3 times, and being obese increased the likelihood of poor sleep quality by 2 times [Table 5]. The model demonstrated an overall accuracy of 77.8%, with a sensitivity of 76.3% for pathologic cases and 79.1% for normal cases [Table 5].

There were no statistically significant differences between the groups in terms of excessive daytime sleepiness, the presence of comorbidities, the number of comorbidities, using antidepressant medication, medication use for MG, the distribution of MG medication groups, MGFA clinical classification, the presence of serum anti-AChR antibodies, and the history of thymectomy [Tables 1 and 2]. These findings underscore the impact of depression, sex, and BMI on sleep quality in patients with MG, highlighting the need for targeted interventions.

Table 4: Correlation analysis between Pittsburgh sleep quality index, myasthenia gravis - quality of life 15, Epworth Sleepiness Scale, Fatigue Severity Scale, beck depression inventory scores, age, and disease duration

	PSQI		MG-QOL15	
	r	*P*	*r*	*P*
Age	−0.045	0.566	−0.128	0.099
Disease duration (months)	−0.103	0.197	−0.082	0.291
BDI	0.420	**<0.001**	0.430	**<0.001**
FSS	0.326	**<0.001**	0.480	**<0.001**
ESS	0.010	0.905	0.039	0.623
MG-QOL15	0.271	**0.001**		

Kendall's tau-*b* test - *r*: Correlation coefficient. Significant *P* values are indicated in bold. PSQI: Pittsburgh sleep quality index, BDI: Beck depression inventory, FSS: Fatigue Severity Scale, ESS: Epworth Sleepiness Scale, MG-QoL15: Myasthenia Gravis Quality of Life Scale

Discussion

Our study revealed that approximately half of the patients with MG experienced poor sleep quality and chronic fatigue. When patients were examined based on sleep quality (good and poor sleep quality), it was observed that patients with poor sleep quality had a low quality of life, a higher rate of depression, and more severe fatigue. Conversely, no statistically significant differences were found between groups regarding excessive daytime sleepiness, comorbidities, various medication uses, the distribution and severity of clinical involvement according to MGFA clinical classification, serum anti-AChR antibody positivity, or thymectomy.

Poor sleep quality has been reported to be common in patients with MG. It has been emphasized that it is particularly more frequent in patients with generalized MG who are not in remission.[13,27] In the study of Martínez-Lapiscina *et al*., it was revealed that disease severity worsened both the quality of life and sleep quality.[13] However, in Tascilar *et al*.'s study, no difference was found in terms of sleep quality between patients with MG and healthy controls.[28] Similar to their findings, we found no significant relationship between disease severity and sleep quality. Our study did not include patients observed in the intensive care unit, those with unstable clinical conditions, and those presenting with myasthenic crisis. Therefore, patients with severe clinical conditions were not recruited. Presumably, there is no relationship between low-to-moderate disease severity and sleep quality.

The literature on excessive daytime sleepiness in patients with MG is conflicting. The frequency of excessive daytime sleepiness in patients with MG varies between 15% and 33%.[10-13] This variation can

Table 5: Evaluation of factors associated with poor sleep quality with logistic regression analysis

	B	SE	*P*	OR	95% OR CI	
					Lower limit	Upper limit
BDI (>10)	−1.884	0.569	0.001	6.580	2.156	20.077
Sex (female)	1.101	0.561	0.049	3.008	1.002	9.034
BMI (obese)	0.704	0.319	0.028	2.021	1.081	3.778
Constant	−0.661	0.729	0.364			

Dependent variable: PSQI predicted (abnormal)=76.3, predicted (normal)=79.1, predicted: 77.8 *P* model <0.001. Multiple logistic regression (method=Backward stepwise [Wald]). CI: Confidence ınterval, *B*: Regression coefficients, SE: Standard error, BDI: Beck depression inventory, BMI: Body mass index, PSQI: Pittsburgh sleep quality index

be attributed to methodologic issues such as differences in sample groups in terms of disease severity. Similar to Nicolle *et al*. and Prudlo *et al*.'s reports, we found no statistically significant relationship between MGFA clinical classification and both sleep quality and excessive daytime sleepiness.[11,12]

Several studies have established a significant relationship between obesity and poor sleep quality in patients with MG.[12] This finding was confirmed in our study as higher rates of obesity were associated with poorer sleep quality. In addition, these studies have emphasized a relationship between corticosteroid use and poor sleep quality. However, in our study, no relationship was found between the use of any type of medication for MG and sleep quality. Similarly, in the study of Martínez-Lapiscina *et al*., no relationship was found between medication groups used for MG and sleep quality.[13]

Our findings are supported in the literature.[28-30] In addition to those mentioned above, we found that fatigue was related to poor sleep quality and low quality of life. It has been reported that depressive disorders are found in approximately one-third of patients with MG.[31] There are many factors affecting the presence of depression and fatigue. Among these is the chronic nature of MG, the adverse effects of the agents used in treatment, the patient's need for assistance in daily life and work life, loss of the patient's independence, and as a result, the negative impact on economic status. The results of studies investigating the relationship between quality of life and sex in patients with MG are contradictory. While our findings suggest a relationship between female sex and poor quality of life in patients with MG, existing literature presents conflicting results, indicating that future research should explore these sex-related disparities further.[30,32,33] The disparity between the studies may be due to methodologic issues such as the number of patients included or clinical staging of patients with MG.

The primary limitations of our study include the reliance on self-reported assessments of sleep quality and the lack of objective measurements such as polysomnography. In addition, the exclusion of patients with severe disease may understate the association between MG and sleep disorders. This necessitates further research on patients with more severe disease states.

Conclusion

Our results indicate that depression, female sex, and obesity are significant predictors of poor sleep quality among patients with MG. Monitoring sleep quality as part of the follow-up care for patients with MG could yield significant benefits in overall disease management. In patients with poor sleep quality, evaluating respiratory functions—especially in female patients—addressing obesity, and treating depression, if present, may enhance adherence to treatment and, consequently, improve QoL in MG. Consequently, it would be reasonable for healthcare providers to incorporate regular assessments of sleep quality into clinical practice for patients with MG to improve adherence to treatment and enhance overall quality of life.

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Conflicts of interest

There are no conflicts of interest.

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