

## QUALITY OF SLEEP IN PATIENTS WITH MYASTHENIA GRAVIS

Jelena Stojanov<sup>1,3</sup>, Aleksandar Stojanov<sup>2,3</sup>, Iva Binić<sup>3</sup>,  
Jovana Antonijević<sup>3</sup>, Martin Popević<sup>4,5</sup>

Myasthenia gravis (MG) is a chronic neuromuscular disease that leads to progressive weakness, fatigue of the skeletal muscles, and is often associated with psychological changes, especially with poorer quality of sleep.

To evaluate the quality of sleep in patients suffering from MG in relation to socio-demographic and clinical characteristics of the disease.

A total of 70 adult patients have been classified according to Myasthenia Gravis Foundation of America classification and divided into groups with regard to the age of onset, gender, employment status and type of work, presence or absence of pathological changes on thymus and presence or absence of anti-nAChR antibodies. Severity of clinical manifestations was evaluated by using quantitative MG scores and MG composite scores. Pittsburgh questionnaire was used to assess the subjective quality of sleep. In addition, Hamilton's anxiety and depression scales and questionnaires for quality of life assessment were also implemented.

The results of our research show a correlation between poor quality of sleep and prolonged duration of the disease, pathological changes on thymus, positive anti-nAChR antibodies. The correlation between poor quality of sleep with more severe clinical presentation, poor quality of life, anxiety and depression was confirmed.

Quality of sleep is impaired in patients with MG, especially in the case of severe clinical manifestations and prolonged duration of the disease. Considering the lack of literature on the subject, a better understanding of the prevalence and severity of sleep disorders in MG requires further research.

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**Key words:** *myasthenia gravis, quality of sleep*

<sup>1</sup>Special hospital for psychiatric illness "Gornja Toponica", Serbia

<sup>2</sup>Clinic of Neurology, Clinical Center of Niš, Niš, Serbia

<sup>3</sup>University of Niš, Faculty of medicine Niš, Niš, Serbia

<sup>4</sup>University of Belgrade, Faculty of medicine Belgrade, Serbia

<sup>5</sup>Institute of Occupational Medicine, Belgrade, Serbia

Contact: Jelena Stojanov  
Special hospital for psychiatric illness "Gornja Toponica",  
Stevana Sindjelića 39, 18202 Gornja Toponica, Serbia  
E-mail: jelena.a.86.ja@gmail.com

### Introduction

Myasthenia gravis (MG) is a chronic neuromuscular disease that causes a disturbance in transmission of nerve impulses to the muscles, which leads to progressive weakness and fatigue of the skeletal musculature (1). MG is a rare neurological disorder, with the prevalence ranging from 15 to 200 out of 1,000,000 persons (2). In Serbia, prevalence is 188.8 out of 1,000,000 persons, which

is one of the highest prevalence reported worldwide (3). It can occur at any age, and is more frequent in women (1.3:1) (3). MG can lead to fatal outcome if it affects respiratory muscles, which as initial manifestation occurs in 1-4% of patients, and the occurrence of this symptom increases to 30-40% at a later stage of the disease (4). Weakness of the intercostal and diaphragmatic muscles leads to the development of dyspnea at rest and sleep disordered breathing (SDB) (5). Obstructive sleep apnea (OSA) is a sleep disorder more common in MG than in other neuromuscular diseases (6). The prevalence of SDB among patients with MG ranges up to 60%, and for OSA is 21.1% (7). Symptoms of breathing disorders develop gradually; they are often unrecognized by patients and are a major cause of mortality in patients with neuromuscular diseases (5, 8). Previous research found a correlation between severity of clinical presentation of MG, accompanied with difficulties in performing daily activities, with poorer quality of life (9, 10).

As a disease with an unpredictable outcome, MG is accompanied by a justified psychological reaction and an increased risk of psychiatric disorders (11, 12). Quality of sleep includes duration and latency of sleep, as well as the degree of rest after

sleep. Sleep quality disturbances are very often present in nearly all psychiatric disorders, particularly in depression and anxiety disorders (13). Little research was done on the relationship between the MG and the quality of sleep, and the interconnectedness is still not clear. It is a fact that evening exacerbations are more frequent in patients with MG, and that affects sleep. In addition, the impaired quality of sleep affects many domains of life in patients with MG. Therefore, it is very important to evaluate the quality of sleep and recognize early manifestations of sleep disorders in these patients.

### **The aim**

The aim of this research was to evaluate the quality of sleep in patients suffering from MG, with regard to socio-demographic and clinical characteristics.

### **Methods**

Study included 70 adult patients treated at the Neurology Clinic, Clinical Center Nis, from December 2016 to December 2017. The diagnosis of MG was made based on data from the patient history, examination, prostigmin and repetitive nerve stimulation test results, as well as by exclusion of other possible causes of symptoms presented. Data on sex, age of onset and current age, employment status, type of work, pathologically altered thymus and presence of anti-nAChr antibodies were collected. Severity of clinical manifestations was evaluated by using quantitative MG scores (QMG) (14) and MG composite scores (MGC) (15). QMG is a 13-item scale that measures ocular, bulbar, respiratory and limb function. It evaluates each finding individually and results range from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits). MGC consists of 10 items and ranks the severity of MG at five levels in relation to the symptomatology and disorder of the affected muscle group function. The maximum score is 50, and the higher score reflects the more difficult form of clinical manifestation.

Patients were divided into groups according to the Myasthenia Gravis Foundation of America (MGFA) classification. Patients from MGFA group V on artificial ventilation were excluded from the study, as well as patients with other chronic illness that could affect the quality of sleep (diabetes, asthma, hypertension, heart failure, renal and hepatic insufficiency.)

PSQI quality of sleep questionnaire consists of 19 self-rated questions. Components of the questionnaire measure quality of sleep, duration and latency of sleep, common efficacy of sleep, and functionality during the day. It assesses a 1-month interval and provides data useful both in clinical and scientific work. In addition to assessing the quality of sleep it provides clinically useful evaluation of variety of factors that might affect quality of sleep. These 19 questions are grouped into seven groups, each scored from 0-3. Obtained global PSQI score is from 0-21, where higher score indicate lower quality of

sleep. It could be used as a tool for measuring interaction of sleep disturbances and depression, as well as relationship between sleep quality and other variables such as age, gender, health status, psychiatric and other medical conditions (13). It is so far the most used quality of sleep questionnaire (16), which is translated and standardized in Serbia (17). PSQI is easy to apply and understandable to patients, and it can potentially be used in everyday clinical practice.

In addition, Hamilton scales for anxiety (HAM-A) and depression (HAM-D) and questionnaires "Questionnaire of Life Quality Specific for Myasthenia Gravis - 15 items" - revised version (MGQOL15r) and Short Form Survey (SF-36), were used.

HAM-D measures the intensity of depression, and the values are interpreted as follows: 0-9 (without depression), 10-13 (mild depression), 14-17 (mild to moderate depression) and 18 or more (moderate to severe depression). HAM-A measures intensity of anxiety, where the ultimate values below 17 indicate absence or mild anxiety, values between 18-24 on mild to moderate anxiety, and values between 25-30 on moderate to severe anxiety.

The MGQOL15r questionnaire measures the quality of life specifically associated with myasthenia gravis. There is no pre-specified cutoff for classification of QoL in MG patients. It consists of 15 questions selected in 4 dimensions (mobility (8 questions), symptoms (3 questions), general contentment (2 questions), and emotional well-being (2 questions)). Each question is assessed from 0 to 4, and higher score represents more significant impact on quality of life.

The SF-36 questionnaire measures the quality of life associated with a general health condition, by including eight general health dimensions: physical functioning (PF), role functional physical (RP), bodily pain (BP), vitality (VT), social functioning (SF), role functioning emotional (RE), mental health (MH), general health (GH), and total score. The total scores for each of the eight dimensions ranged from 0 to 100 on the scale, where a higher score represents better health.

All patients signed an informed consent for participating in the study.

All data were statistically analyzed by IBM SPSS (version 21) for Windows operative system. Results with  $p < 0.05$  were considered statistically significant. Numerical data were presented as means  $\pm$  SD. The Mann-Whitney test was used to compare continuous variables between the two groups, and the Kruskal-Wallis test was used for comparison of more than two groups. Correlations were assessed using Pearson's correlation coefficients or Spearman's correlation coefficients.

### **Results**

Epidemiological and clinical characteristics of 70 patients are presented in Table 1. The scores obtained by the used questionnaires are presented in Table 2.

**Table 1.** Demographic and clinical characteristics of MG patients

Variable	Value
Gender (number of patients)	
Male	33 (47.1 %)
Female	37 (52.9 %)
Current age (years) (Mean $\pm$ SD)	53.16 $\pm$ 15.98
Disease duration (years) (Mean $\pm$ SD)	4.45 $\pm$ 4.4
Profession (number of patients)	
Physical workers	16 (22.9 %)
Intellectual workers	13 (18.6 %)
Unemployed	13 (18.6 %)
Retired	28 (40.0 %)
First MG symptoms (number of patients)	
<50	35 (50%)
$\geq$ 50	35 (50%)
Thymus pathology (number of patients)	
absent	25 (36%)
present	45 (64%)
Anti nAChR antibodies (number of patients)	
absent	14 (20%)
present	56 (80%)
Current MGFA* (number of patients)	
I	15 (21.4 %)
IIa	11 (15.7 %)
IIb	16 (22.9%)
IIIa	8 (11.5 %)
IIIb	10 (14.4%)
IVa	6 (8.5%)
IVb	4 (5.7%)
QM <sup>+</sup> (Mean score $\pm$ SD)	8.16 $\pm$ 15.67
MGC <sup>#</sup> (Mean score $\pm$ SD)	7.51 $\pm$ 5.33

\* Myasthenia Gravis Foundation of America (MGFA)

<sup>+</sup> Quantitative myasthenia gravis score (QM<sup>+</sup>)

<sup>#</sup> Myasthenia gravis composite scores, (MGC)

**Table 2.** Scores for all patients obtained on the used questionnaires

PSQI*	6.76 $\pm$ 4.60
Hamilton scale for depression (Mean score $\pm$ SD)	10.29 $\pm$ 6.34
Hamilton scale for anxiety (Mean score $\pm$ SD)	9.5 $\pm$ 6.9
MGQOL15r <sup>+</sup>	22.5 $\pm$ 11.53
SF36 scores <sup>#</sup>	
physical functioning	58.28 $\pm$ 38.39
role functional physical	43.59 $\pm$ 49.6
vitality	58.09 $\pm$ 47.71
mental health	57.43 $\pm$ 25.23
role functioning emotional	65.37 $\pm$ 18.9
social functioning	69.65 $\pm$ 26.28
bodily pain	70.64 $\pm$ 26.52
general health	50.28 $\pm$ 10.03
Sum score	57.5 $\pm$ 24.7

\* Pittsburgh Sleep Quality Index (PSQI)

<sup>+</sup> Questionnaire of Life Quality Specific for Myasthenia Gravis - 15 items "- revised version (MGQOL15r)

<sup>#</sup>Study Short Form of 36 questions (SF36)

(a) Differences in sleep quality in relation to different socio-demographic and clinical characteristics

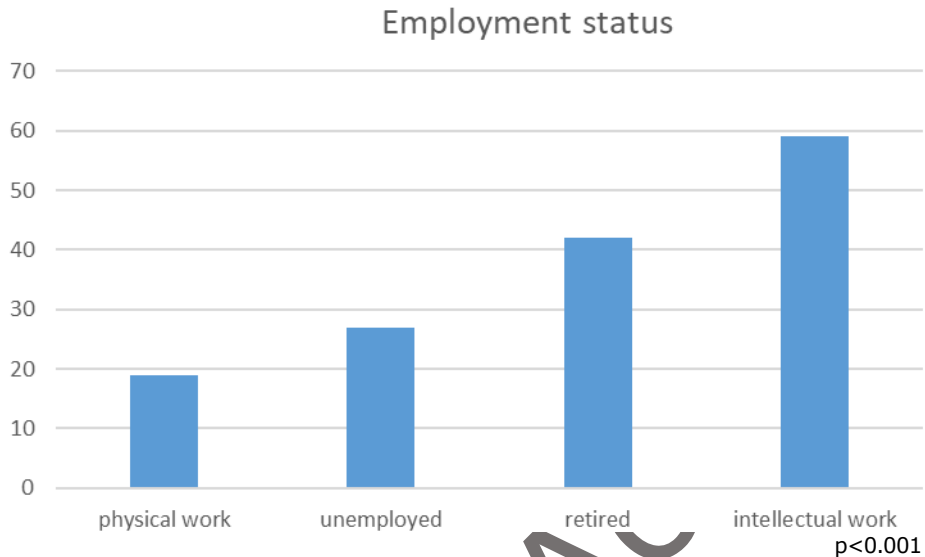
In relation to gender, early or late onset of the disease, a statistically significant difference was not found in quality of sleep. Statistically significant difference with regard to quality of sleep exists in

patients with pathological changes on the thymus, compared to the group of patients without these changes ( $p < 0.001$ ). There is also a clear statistical difference between the groups with positive anti-nAChR antibodies (lower sleep quality) compared to the group of seronegative patients ( $p < 0.001$ ). With regard to employment status and the type of work,

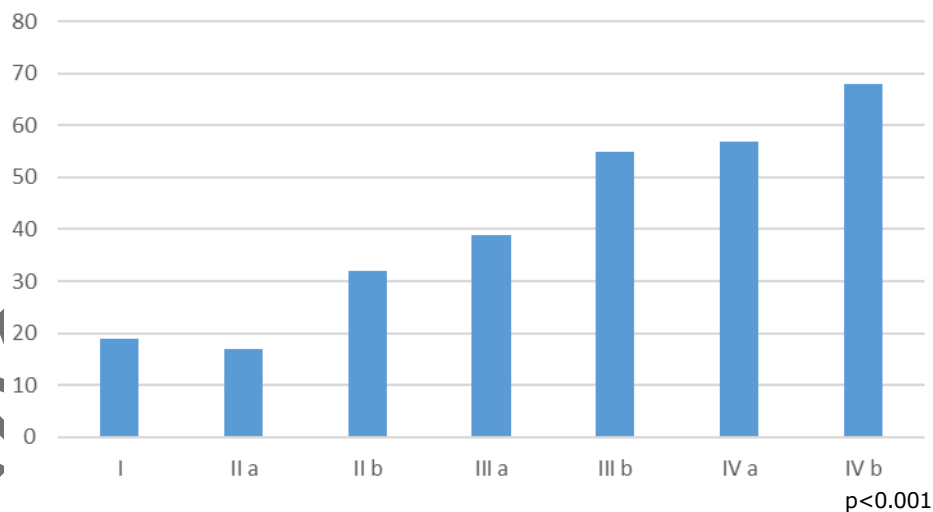
the worst sleep quality was observed in physical workers, and the best in intellectual or administrative workers, with a statistically significant ( $p < 0.001$ ) difference between the groups (Graph 1.).

(b) Correlation analysis between the severity of the clinical manifestation and the quality of sleep

In comparison with MGFA classification, patients with severe clinical presentation had the lowest quality of sleep, and this was more pronounced in groups with bulbar symptomatology, with statistically significant difference (Graph 2.).



**Graph 1.** Mean rank PSQI scores (Kruskal-Wallis test) in relation to employment status



**Graph 2.** Mean rank PSQI scores (Kruskal-Wallis test) in relation to MGFA classification

In relation to the assessment of the severity of the clinical presentation, there is a clear correlation between more severe clinical manifestation and lower quality of sleep (Table 3.). Age and PSQI showed no clear correlation ( $p = 0.62$ ), but the correlation was shown between the prolonged duration of disease and lower quality of sleep ( $p < 0.001$ ).

Comparing other applied scales, a clear correlation was found between estimated lower quality of sleep and lower quality of life, anxiety and depression (Table 4.). Statistically significant correlation was shown between most of the sub-scales on the SF36 questionnaire and a questionnaire that assess the quality of sleep (for psychical functioning, role functioning emotional and general

health  $p < 0.001$ ; and for mental health, social functioning and bodily pain  $p < 0.05$ ).

**Table 3.** Correlation of sleep quality with duration of disease and severity of clinical picture

	Duration of illness		MGC <sup>+</sup>		QMC <sup>#</sup>	
	R	p	R	p	R	p
PSQI*	0.382	<0.001**	0.734	<0.001**	0.694	<0.001**

$p < 0.001^{**}$

- <sup>+</sup> Myasthenia gravis composite scores (MGC)
- <sup>#</sup> Quantitative myasthenia gravis score (QMC)
- \* Pittsburgh Sleep Quality index (PSQI)

**Table 4.** Correlation of sleep quality with quality of life, depression and anxiety

	MGQOL15r <sup>+</sup>		SF36 <sup>#</sup>		Hamilton scale for depression		Hamilton scale for anxiety	
	R	p	R	p	R	p	R	p
PSQI*	0.659	<0.001**	-0.404	<0.001**	0.612	<0.001**	0.596	<0.001**

$p < 0.001^{**}$

<sup>+</sup> Questionnaire of Life Quality Specific for Myasthenia Gravis - 15 items "- revised version (MGQOL15r)

<sup>#</sup> Study Short Form of 36 questions (SF36)

\* Pittsburgh Sleep Quality Index (PSQI)

## Discussion

In accordance with the aim of the study, the results show the correlation between poor quality of sleep and severity of clinical manifestation in MG, prolonged duration of the disease, pathological changes on thymus, the presence of positive anti-nAChr antibodies, poor quality of life and the presence of anxiety and depressive symptomatology in patients with MG.

Although daytime sleepiness and fatigue are common symptoms in neuromuscular diseases, there is not much data on the quality of sleep in these patients (18). Previous studies identified a higher prevalence of daytime sleepiness among MG patients (19, 20), while others found correlation only with the generalized type of the disease (21). Happe et al. (22) have found a association between the severity of clinical manifestations in MG and low quality of sleep, which is in line with the results of our research, while other studies have not established this association (6, 7). Studies that failed to find association between MG and poor quality of sleep had restriction in a form of small statistical samples (21, 23).

The results of our research show a correlation between lower quality of sleep and prolonged duration of the disease, which has never been examined, according to the available literature.

Tascilar et al. (24) found correlation between lower quality of life and PSQI scores only with regard to subjective sleep duration, and the results of our research have determined the correlation between the scores obtained on the PSQI questionnaire and

the scores on the questionnaires that assess the quality of life (MG-QOL15). By using the SF-36 questionnaire for assessing the quality of life, Basta et al. (25) found negatively affected mental aspects of SF-36 in patients with MG, while the results of our research determined the correlation between the majority of the sub-scales on the SF-36 questionnaire and the PSQI questionnaire.

Sleep quality disturbances, including difficulty falling asleep or difficulty in maintaining sleep, are very often present in nearly all psychiatric disorders, particularly in depression and anxiety disorders (12). The weakness of skeletal musculature in patients with MG is often accompanied by depressive and anxiety symptomatology (26, 27), as well as impaired quality of life (28). In our research, lower quality of sleep correlated with the intensity of depressive and anxiety symptomatology in patients with MG. Some studies found no correlation between the duration of sleep and depression or anxiety (29), nor the correlation between the severity of MG and anxiety disorders (30).

Our results show association between pathological changes on thymus with poorer quality of sleep. The results also show correlation between lower quality of sleep and presence of anti-nAChr antibodies, which has not been compared in previous research. Magni et al. (31) have not found association between psychiatric disturbances in MG with pathological changes on thymus, thymectomy, or age of MG onset, and also they did not evaluate the quality of sleep.

Most of these results indicate the significant role of MG in the daily functioning and the fulfillment

of social tasks. This is the first study of quality of sleep in patients with MG in Serbia, based on relevant and validated sleep quality questionnaire. Restrictions include a small sample and the fact that we did not perform polysomnography to verify these patient-reported disturbances of sleep.

### Conclusion

The results of our study showed a correlation between poor quality of sleep and prolonged duration of the disease. The link between pathological changes on thymus and the presence of positive anti-nAChr antibodies with poor quality of sleep was also demonstrated. Our results confirm

the correlation between lower quality of sleep with more severe clinical presentation, poor quality of life and the presence of anxiety and depressive symptomatology in patients with MG. It is our suggestion that scale for assessing the quality of sleep (PSQI) should be used in the daily clinical work, considering that it is easily applied, understandable to patients and provides a clinically useful assessment of various factors that can affect quality of sleep. Considering the lack of literature on the subject, better understanding of the prevalence and severity of sleep disorders in MG requires further research.

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**KVALITET SPAVANJA KOD BOLESNIKA SA MIJASTENIJOM GRAVIS**

*Jelena Stojanov<sup>1,3</sup>, Aleksandar Stojanov<sup>2,3</sup>, Iva Binić<sup>3</sup>,  
Jovana Antonijević<sup>3</sup>, Martin Popević<sup>4,5</sup>*

<sup>1</sup>Specijalna bolnica za psihijatrijske bolesti "Gornja Toponica", Srbija

<sup>2</sup>Klinika za neurologiju, Klinički centar Niš, Srbija

<sup>3</sup>Univerzitet u Nišu, Medicinski fakultet Niš, Srbija

<sup>4</sup>Univerzitet u Beogradu, Medicinski fakultet Beograd, Srbija

<sup>5</sup>Institut za medicinu rada Srbije, Beograd, Srbija

*Kontakt:* Jelena Stojanov

Specijalna bolnica za psihijatrijske bolesti "Gornja Toponica", Stevana Sindelića 39, 18202 Gornja Toponica, Srbija

E-mail: jelena.a.86.ja@gmail.com

Miastenija gravis (MG) je hronična neuromišićna bolest koja dovodi do progresivnog zamora, slabosti skeletnih mišića i često je povezana sa psihičkim izmenama, posebno sa lošijim kvalitetom spavanja.

Proceniti kvalitet spavanja kod pacijenata koji boluju od MG u odnosu na sociodemografske i kliničke karakteristike oboljenja.

Ukupno 70 odraslih bolesnika su klasifikovani prema Klasifikaciji Američke fondacije za MG i podeljeni su u grupe u odnosu na starost kada su tegobe počele, pol, zaposlenost i vrstu posla kojim se bave, prisustvo ili odsustvo patoloških promena na timusu i prisustvo ili odsustvo anti-nAChR antitela. Težina kliničkog ispoljavanja je prcenjena korišćenjem kvantitativnog MG skora i MG kompozitnog skora. Pored Pitsburgovog upitnika za procenu kvaliteta spavanja, korišćene su i Hamiltonove skale za procenu anksioznosti i depresije i upitnici za procenu kvaliteta života.

Rezultati našeg istraživanja su pokazali korelaciju između lošijeg kvaliteta spavanja i dužeg trajanja bolesti, patoloških promena na timusu, pozitivnih anti-nAChR antitela. Potvrđena je korelacija između lošijeg kvaliteta spavanja sa težom kliničkom slikom, lošijim kvalitetom života, anksioznošću i depresijom.

Kvalitet spavanja je narušen kod pacijenata sa MG, posebno kod težeg kliničkog ispoljavanja i dužeg trajanja bolesti. U odsustvu literature, bolje razumevanje prevalence i ozbiljnosti poremećaja spavanja u MG zahteva dalja istraživanja.

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**Ključne reči:** miastenija gravis, kvalitet spavanja