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ORIGINAL ARTICLE

# Characteristics of obstructive sleep apnea in myasthenia gravis patients: a single center study

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## Abstract

**Background** Recent studies have shown a high prevalence of obstructive sleep apnea in myasthenia gravis compared to the normal population. The aim of this study was to elucidate clinical and polysomnographic differences between clinically stable Korean MG patients with and without OSA.

**Methods** A total of 18 consecutively stable MG patients were included in this prospective study. We compared MG patients with OSA ($n = 7$) and without OSA ($n = 11$) with respect to the baseline characteristics and overnight polysomnography (PSG) parameters. Demographic parameters, prescribed medication status, thymectomy status, myasthenia gravis foundation of America score, and antibody status were obtained from their medical records. We performed the Korean version of Pittsburg sleep quality index to assess the subjective quality of sleep. Statistical analyses were performed using SPSS version 18.0 with Wilcoxon rank sum test, chi-square test, Fisher's exact test, and Spearman correlation test.

**Results** Among the clinical parameters, MG patients with OSA showed a higher proportion of male sex ($p = 0.016$) and increased body mass index ($p = 0.033$). The PSG showed an 11-fold higher supine apnea-hyponea index (AHI) in MG patients with OSA. AHI was further analyzed with supine and non-supine position. MG patients with OSA had a higher supine AHI ($19.5 \pm 15.8$) compared to those without OSA ($1.9 \pm 1.2$, $P = 0.008$). Most of MG patients with OSA (85.7%) showed more than two times higher supine AHI than non-supine AHI.

**Conclusions** This study showed that the occurrence of OSA in patients with MG is associated with male sex and obesity, which is in accordance with the normal population. Moreover, PSG data showed a high prevalence of supine dominant OSA in MG patients with OSA.

**Keywords** Myasthenia gravis · Sleep apnea · Obstructive · Male · Body mass index

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that involves pathological changes in the postsynaptic neuromuscular junction, causing neuro-transmission defects. The prevalence of MG is estimated at 17 to 21 per 100,000 population in a Caucasian systemic review [1], and a recent Korean study showed a prevalence rate of 13 per 100,000 population [2]. It is clinically characterized by diurnal fatigability, ptosis, diplopia, dysarthria and rarely, respiratory failure. Obstructive sleep apnea (OSA) is known to cause hypoxia and hypercapnia that leads to excessive daytime sleepiness, and it is also known to be associated with cardiovascular comorbidities and metabolic dysfunction [3]. About 70% of MG patients are generalized, and 30–40% of the MG patients are known to develop respiratory muscle weakness, including oropharyngeal muscles leading to sleep-disordered breathing [4, 5]. Until now, only a few studies have investigated the association of OSA with MG, which reported a higher prevalence rate of OSA, with a rate of 36 to 64% when compared to the normal population [6, 7]. However, these studies focused on the differences in OSA prevalence between the normal and MG population. Further, these studies included various stages

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of MG patients. The present study aimed to find the characteristics of OSA in MG and to elucidate the clinical and polysomnographic differences between clinically stable Korean MG patients with and without OSA.

## Methods

This was a prospective study, and patients with stable MG who gave their written consent were consecutively recruited from the Department of Neurology at Kyungpook National University Chilgok hospital, between years 2016 and 2017. The patients received blood tests, polysomnography, and questionnaires at the time of the enrollment. Our center covers Kyungpook province that has a population of five million people in South Korea. The diagnosis of MG was based on clinical symptoms with at least one of the following objective findings: (1) positive electrophysiological assessment of repetitive nerve stimulation test that showed a decremental response of more than 10%, or (2) positive findings for acetylcholine receptor antibody/MuSK antibody levels or (3) positive findings following pyridostigmine injection test. Among the clinically diagnosed MG patients, the inclusion criteria were (1) stable patients with no progressive changes in the clinical condition for more than 6 months, (2) patients with a low dosage of steroids (less than 10 mg) and no changes in the medication for more than 6 months, and (3) patients who gave informed consent for the study. The exclusion criteria were (1) MG patients previously diagnosed with sleep disorders, (2) patients who were on medication that may affect the sleep parameters, and (3) patients with other psychiatric disorders. This study was approved by the International Review Board of Kyungpook National University Chilgok Hospital, and informed consent was taken from all patients who participated in this study.

We used Myasthenia Gravis Foundation of America (MGFA) scale to evaluate the clinical severity of the patients [8]. The MGFA scale is classified into five scales. Class I is defined when the patient has only ocular symptoms without weakness, class II to IV are classified into mild, moderate, and severe weakness; and class V is defined when the patient is on intubated state. According to this MGFA classification, we enrolled stable MG patients, with an MGFA classification of one or two. The Apnea-Hypopnea index (AHI) is a valuable index that represents the number of apnea and hypopnea events during sleep. It is divided into four scales according to the index number that represents the number of sleep apnea events. AHI of less than five is normal, AHI index between 5 and15 is mild, AHI index between 15 and 30 is moderate and AHI of more than 30 is severe [9].

### Clinical parameters

Clinical parameters, such as sex, age, duration of the disease, prescribed medication status, and thymectomy status were obtained from the patients' medical records. The acetylcholine receptor binding antibody and anti-MuSK antibody status were checked, and body mass index (BMI) was calculated for all the enrolled patients. The patients were also evaluated for the pulmonary function test via conventional methods, which included forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1).

### Polysomnographic parameters

Single-night polysomnography (Beehive Millennium, Grass-Telefactor, USA) was performed on all the enrolled patients. The product of Grass-Telefactor has been its usefulness and good performance and is globally used [10], and Beehive Millennium is an updated product for recording EEG and sleep events. All PSG parameters were scored by an experienced PSG technologist and confirmed by a sleep specialist. The parameters, settings, filters, technical specifications, sleep stage scoring, and event scoring were defined based on the AASM manual for scoring of sleep and associated events [11]. OSA was defined as mentioned previously [12]. PSG scoring for the parameters of OSA has been established its strong validity and reliability and is the current gold standard for defining the presence and severity of OSA [11, 13] AASM guideline which was used in this study showed substantial interrater agreement in the scoring the sleep parameters [13].

We further analyzed supine and non-supine OSA from the PSG data. Supine OSA was defined based on two conditions: (1) an Apnea-Hypopnea index (AHI) greater than 5 events/h and (2) the frequency of respiratory events being more than twice higher when compared to non-supine position [11].

The Korean version of Pittsburgh Sleep Quality Index (PSQI-K) was used to evaluate the quality of sleep in MG patients, along with the overnight polysomnography [14]. We also performed Korean Epworth sleepiness scale (KESS) to evaluate the sleep disordered breathing in MG patients [15].

### Statistical analysis

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc. Chicago, IL, USA). Comparison between the groups (MG with OSA vs MG without OSA) was performed using the Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Spearman correlation test was used to evaluate the correlation between the AHI and other clinical parameters. The results were presented as mean ± standard deviation. A $p$ value $< 0.05$ was considered statistically significant.

## Results

A total of 20 patients were initially enrolled after satisfying all the inclusion and exclusion criteria, but two patients were finally excluded due to follow-up loss and withdrawal of the consent. Total of nine males and nine females were recruited with a mean BMI of 23.7 ± 3.4 kg/m$^2$ and mean AHI of 10.4 ± 14.1. Other baseline characteristics of the 18 MG patients enrolled in the study are listed in Table 1. The mean age was 49.6 ± 11.1 years with a mean follow-up of 6.7 ± 5.3 years. All the patients enrolled were classified as MGFA class 1 or 2 (13 and 5 patients, respectively). Out of the 18 patients, five patients were on steroids (less than 10 mg), that accounted for 27.8% of the patients, and 12 patients were on immunosuppressant medication. Further, eight patients had a history of thymectomy (44.4%). Mean FVC and FEV1 for all the patients were 81.9 ± 16.8 and 88.0 ± 14.1, respectively. The mean BMI of the patients was 23.7 ± 3.4 kg/m$^2$ and mean AHI was 10.4 ± 14.1 with the prevalence of OSA being 38.9% (7 out of 18 patients). Among these seven patients, two patients showed mild, three patients showed moderate, and two patients showed severe OSA.

### Characteristics of MG patients with OSA

We compared MG patients with and without OSA with respect to the baseline characteristics and overnight PSG parameters. Among the clinical parameters, male sex, and BMI showed a statistically significant difference between MG patients with and without OSA groups (6 vs 3, $p = 0.016$ in male sex; 26.0 ± 3.4 vs 22.2 ± 2.7, $p = 0.033$ in BMI). The age at onset and disease duration showed no significant difference between the two groups ($p = 0.051$, $p = 0.928$, respectively). Moreover, there was no significant difference between the groups and their status related to thymectomy. (Table 2).

**Table 1** Patient characteristics at baseline (*n*; 18)

| Variables | Number or mean ± SD |
|---|---|
| Gender, male/female | 9/9 |
| Age, years | 49.6 ± 11.1 |
| Follow-up periods, years | 6.7 ± 5.3 |
| MGFA classification 0/1 | 13/5 |
| Acetylcholine receptor antibody positive | 14 (77.8%) |
| MuSK receptor antibody positive | 1 (5.6%) |
| Steroid medication less than 10 mg | 5 (27.8%) |
| Use of immunosuppressant | 12 (66.7%) |
| Pulmonary function test | |
| FVC | 81.9 ± 16.8 |
| FEV1 | 88.0 ± 14.1 |
| FEV1/FVC | 1.1 ± 0.1 |
| History of thymectomy | 8 (44.4%) |

Data were expressed by number or mean ± SD (standard deviation). *MGFA*, myasthenia gravis foundation of America; *FVC*, forced vital capacity; *FEV1*, forced expiratory volume at first second

### Polysomnography data of MG with OSA

Among the PSG parameters, AHI in MG with OSA was 23.6 ± 15.1 while AHI in MG without OSA patients was 1.9 ± 1.2 ($r = 0.728$, $p < 0.001$). We further analyzed AHI with supine and non-supine position, and interestingly, supine AHI index was 10.8-fold higher in the OSA patients ($p = 0.008$). Furthermore, no significant changes were observed between the two groups, in terms of total sleep time (TST) and wake after sleep onset (WASO), sleep efficacy, and sleep onset latency ($p = 0.684$, $p = 0.390$, $p = 0.650$, $p = 0.441$, respectively). Our result showed no difference in REM sleep between the two groups ($p = 0.651$). Furthermore, NREM sleep was subdivided into N1, N2, and N3 but showed no statistically significant difference between the two groups in all stages of NREM.

### The relationship between PSQI-K and KESS scores in MG patients

We also performed PSQI-K to evaluate subjective sleep quality of MG patients and as demonstrated in Table 2, there was no significant difference between the groups or correlation in the total score ($r = -0.034$, $p = 0.907$). The KESS also showed no relationship between MG patients with and without OSA ($r = 0.097$, $p = 0.703$).

## Discussion

We found male sex and BMI as statistically significant influential factors between MG with and without OSA groups. Several studies have reported male sex and BMI as independent risk factors for OSA in the normal population [16, 17] in accordance with our result. Although, the higher prevalence of OSA in men needs to be explored further, we attempted an explanation based on several existing hypotheses to extrapolate it. The disparity can partly be explained by the differences in sex-related hormones and the upper airway anatomy [17, 18]. Along with the male sex being a risk factor for OSA, a close association between high BMI and OSA also been reported in the literature, and weight reduction has been found to reduce the severity of OSA [17, 18]. An observational study on MG also demonstrated similar results, illustrating a high prevalence of OSA and concluding old age and increased BMI to be the potential risk factors [19]. Our result is in line with these results as the BMI was a statistically significant factor for OSA in the current study.

**Table 2** Comparison of the baseline characteristics and overnight polysomnography parameters in myasthenia gravis patients with and without obstructive sleep apnea

| | MG with OSA ($n = 7$) | MG without OSA ($n = 11$) | $p$ value |
|---|---|---|---|
| Male sex | 6 (86%) | 3 (27%) | 0.016* |
| Age at onset, years | 47.4 (9.7) | 39.8 (9.0) | 0.051 |
| Disease duration, years | 5.9 (2.9) | 7.3 (6.5) | 0.928 |
| History of thymectomy | 3 (43%) | 5 (45%) | 0.914 |
| Body mass index, kg/m$^2$ | 26.0 (3.4) | 22.2 (2.7) | 0.033* |
| NREM1 | 16.0 (8.7) | 14.7 (6.1) | 0.751 |
| NREM2 | 60.4 (10.7) | 57.0 (8.8) | 0.319 |
| NREM3 | 5.2 (4.7) | 10.9 (8.0) | 0.147 |
| REM sleep phase | 18.4 (6.6) | 17.6 (4.7) | 0.651 |
| Total arousal index | 21.6 (10.3) | 17.3 (8.4) | 0.298 |
| Apnea-hypopnea arousal index | 15.1 (8.9) | 3.1 (4.7) | 0.002* |
| Snore arousal index | 1.6 (1.9) | 1.7 (3.9) | 0.596 |
| TST | 379.6 (21.6) | 373.5 (67.9) | 0.684 |
| WASO | 59.0 (30.6) | 46.9 (29.1) | 0.390 |
| Sleep efficiency | 85.6 (6.7) | 86.5 (8.0) | 0.650 |
| Sleep onset latency | 5.0 (2.9) | 8.9 (8.3) | 0.441 |
| PSQI-K | 7.7 (4.5) | 7.0 (5.0) | 0.948 |
| C1 | 1.3 (0.8) | 1.5 (0.8) | 0.950 |
| C2 | 1.3 (1.2) | 1.5 (1.1) | 0.852 |
| C3 | 1.3 (1.2) | 1.1 (1.4) | 0.755 |
| C4 | 0.5 (0.8) | 0.9 (1.4) | 0.755 |
| C5 | 1.5 (0.5) | 1.1 (0.4) | 0.282 |
| C6 | 0.5 (1.2) | 0.0 (0.0) | 0.662 |
| C7 | 1.2 (0.8) | 0.9 (0.8) | 0.573 |
| AHI | 23.6 (15.1) | 1.9 (1.2) | < 0.001* |
| Supine | 19.5 (15.8) | 1.8 (1.3) | 0.008* |
| Non-supine | 4.9 (8.8) | 1.1 (1.8) | 0.536 |

Data were expressed by number (%) or mean (standard deviation). *MG*, myasthenia gravis; *OSA*, obstructive sleep apnea; *NREM*, sleep stage without rapid eyes movement; *TST*, total sleep time; *REM*, rapid eyes movement; *WASO*, wakefulness after sleep onset; *PSQI-K*, Korean version of Pittsburgh Sleep Quality Index; *AHI*, apnea-hypopnea index

*$p < 0.05$

OSA is a multifactorial disease, and notably, the OSA observed in MG is more complicated, since there is clinical evidence for the reversibility of OSA via plasmapheresis or thymectomy [18, 20], indirectly reflecting disease severity as an additional factor for OSA, that needs to be considered. Respiratory muscle weakness and fatigue also play an important role in MG, owing to the involvement of diaphragm and accessory ventilatory muscles. Respiratory symptoms are among the core clinical manifestations of MG; and out of these, sleep apnea is one of the crucial factors that impact the quality of life and influence the clinical status of MG [21, 22]. Moreover, recent studies on MG have also reported oropharyngeal muscle weakness, which affects the upper airways, leading to its collapse and causing obstruction [3, 6]. One study reported abnormal abduction and adduction of the vocal cords, eventually leading to deepening of the voice, dysarthria, and increased oropharyngeal muscle weakness [23, 24]. In a recent study on OSA in the normal population, approximately 50% of the patients had supine dominant OSA with higher mortality and morbidity risk factors [25]. In our results, five out of seven patients (71%) showed supine OSA, which is higher than the prevalence found in the normal population. Therefore, our study supports the relevance of oropharyngeal weakness in MG, as this muscle group is mostly affected during the supine position [26]. Moreover, our result showed 11-fold higher supine OSA as compared to non-supine OSA (19.5 ± 15.8 vs 1.8 ± 1.3) in MG patients with sleep apnea, with a prevalence of 70%; which is higher than that in the normal population. Although the pathogenesis of supine OSA is not clearly understood, one of the widely accepted hypotheses suggests narrowing of the oropharyngeal airway, which is known to be significantly reduced in MG and is also in line with our PSG results [26].

We additionally investigated PSQI-K and KESS that reflect the quality of sleep and sleep disordered breathing in MG. The total score and the sub scores of PSQI-K and KESS showed no difference between the two groups, demonstrating the limitations of PSQI-K and KESS in evaluating sleep disordered breathing and OSA in these MG patients, in contrast to the overnight PSG, which appears to be a more sensitive tool for the diagnosis. However, this remains to be further validated.

Our study has a few limitations that need to be addressed. Firstly, this was a single-center study reflecting a relatively small population, thus imploring the need for external validity. Secondly, the power of explanation is reduced by the small number of patients enrolled due to the cost considerations for the overnight PSG studies. Thirdly, we enrolled stable MG patients with MGFA of 1 or 2 and therefore, our data reflects the sleep disturbances observed specifically in the mild MG patients. Lastly, we did not confirm the existence of oropharyngeal weakness in MG via objective tests, such as manometer or endoscopy, to confirm the hypothesis.

## Conclusion

To our knowledge, this is the most extensive data from the stable MG populations, containing detailed overnight PSG evaluation, which is currently used as a golden diagnostic tool for OSA. We found male sex and the BMI to be relevant factors for OSA in MG, which is in accordance with the normal population, but with a higher prevalence rate. Furthermore, supine dominant OSA was more frequently observed in MG with OSA, and although further studies are needed to understand the pathophysiology, proper treatment strategies for OSA in MG may be applied based on our results, that may eventually lead to better quality of sleep in stable MG patients.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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