

Sleep disorders in patients with myasthenia gravis: a systematic review

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Abstract. [Purpose] This systematic review evaluated the presence of sleep-disordered breathing in patients with myasthenia gravis and clarified the role of physiotherapy. [Subjects and Methods] We followed the PRISMA declaration criteria. The evaluation was performed in accordance with the STROBE statement for observational and cross-sectional studies and the CONSORT checklist for clinical trials. Searches were followed by hand on MEDLINE, EMBASE, SciELO, PubMed Central, and the Cochrane Central Register of Controlled Trials. [Results] Our searches yielded a total of 36 studies published between 1970 and 2014. The number of patients involved ranged from 9–490. Of the 36 studies, 19 articles were excluded because they did not meet the inclusion criteria. Therefore, 17 observational, cross-sectional, or clinical studies assessing the quality of sleep and prevalence of sleep disorders in patients with myasthenia gravis were eligible for our review. [Conclusion] Some studies of patients with MG show that patients with MG are associated with poor sleep quality, excessive daytime sleepiness, presence of restless syndrome, and a higher incidence of SDB, while other studies do not report such associations. Therefore, given the current inconclusive evidence and limited literature, further study of sleep disturbances in patients with MG is needed.

Key words: Myasthenia gravis, Neuromuscular disorders, Obstructive sleep apnea

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune chronic neuromuscular disease that causes weakness and fatigue of the skeletal muscles. The weakness is caused by impaired transmission of nerve impulses to the muscles. The nerve conduction of muscle fibers is represented by the velocity of propagation of action potentials triggered from a neuromuscular junction along the muscular fiber, generating a twitch^{1–3)}; this conduction velocity varies with fatigue and the type of compromised muscle fiber²⁾. MG is rarely fatal but can be life threatening when it affects the muscles required for swallowing and ventilation. The first symptom of the disease is weakness of the eye muscles, which may progress to stagnation or weakness of the muscles involved in swal-

lowing, phonation, and mastication or even limb muscles. MG affects 1 in 10,000 Americans between 20 and 40 years of age, with women affected more often than men (gender ratio: 3:2)⁴⁾.

MG is usually classified as acquired, congenital, or neonatal persistent. The acquired form, which is the most common, can occur at any age after birth. In 1971, Osserman proposed a clinical classification of the severity of adult myasthenia: I, II-A, II-B, III, or IV. The classification is based on symptom onset, symptom severity, and anatomical distribution of the affected muscle groups⁵⁾.

Approximately 70% of patients with MG have generalized MG in categories II-A and II-B. In the initial disease phase, only 1–4% of patients have dysfunction of the ventilatory muscles; however, in the later stages, 30–40% of patients will develop some level of ventilatory muscle involvement⁶⁾.

Among the clinical manifestations of MG, the emergence of sleep-disordered breathing (SDB) due to weakening of the oropharyngeal muscles strongly impacts patient quality of life. Furthermore, symptoms of SDB usually develop gradually, which often makes patients unaware of them. However, sleep disorders, particularly SDB, are major causes of morbidity and mortality in patients with neuromuscular

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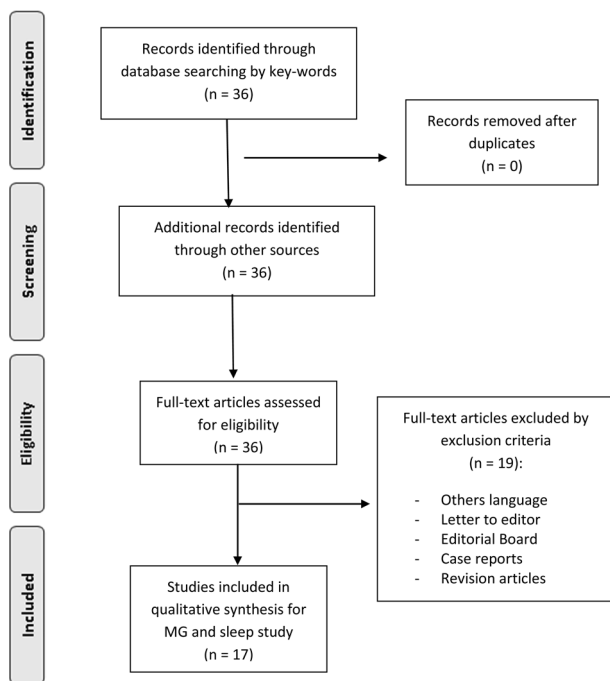


Fig. 1. Selection process for studies included in this systematic review
MG: myasthenia gravis

diseases⁷⁻⁹). This systematic review was conducted to determine what is known about the presence of sleep disorders on MG patients.

Therefore, it is important that health professionals, particularly physiotherapists, recognize the early manifestations of sleep disorders in patients with neuromuscular diseases so that they can intervene with noninvasive ventilatory support and improve quality of life¹⁰.

METHODS

Searches were conducted using MEDLINE, EMBASE, SciELO, PubMed Central, and the Cochrane Central Register of Controlled Trials. The searches were performed using the following key words: (“myasthenia gravis” OR “neuromuscular disease”) AND (“sleep” OR “sleep quality” OR “sleep apnea” OR “obstructive sleep apnea” OR “central sleep apnea” OR “restless legs syndrome” OR “sleep disorder” OR “sleep disordered breathing”). The medical subject headings search filter was used. Literature searches were concluded on October 24, 2014.

Two independent reviewers performed the first round of study screenings on the basis of information in the title, abstract, and keywords. In cases of disagreement between reviewers, a third reviewer was consulted to help reach a consensus. After conducting the literature searches, the reviewers independently read the retrieved literature.

The inclusion criterion for this systematic review was a randomized controlled trial, non-controlled cross-sectional study, or observational article involving patients with MG and assessing the presence of sleep disorders. All literature

Table 1. STROBE statement scores

Authors and year of publication	Study design	STROBE score
Mennuni et al. 1983	Cross-sectional	19/22
Stepansky et al. 1997	Cross-sectional	19/22
Quera-salva et al. 1992	Cross-sectional	22/22
Lapiscina et al. 2011	Cross-sectional	21/22
Happe et al. 2004	Cross-sectional	21/22
Nicolle et al. 2005	Cross-sectional	18/22
Sleminki et al. 2012	Cross-sectional	21/22
Prudloa et al. 2007	Cross-sectional	20/22
Kassardjian et al. 2012	Cross-sectional	18/22
Elsais et al. 2013	Cross-sectional	22/22
Manni et al. 1995	Cross-sectional	20/22
Papazian et al. 1976	Cross-sectional	19/22
Yeh et al. 2013	Cross-sectional	19/22

Table 2. CONSORT checklist scores

Authors and year of publication	Study design	CONSORT score
Amino et al. 1998	Clinical trial	19/25
Sonka et al. 1996	Clinical trial	20/25
Qiu et al. 2010	Clinical trial	21/25
Ito et al. 2010	Clinical trial	23/25

included in the present study was published between 1970 and 2014. Review articles, abstracts, study protocols, letters to the editor, technical notes, case reports, and articles written in languages other than English were excluded.

This systematic review followed the criteria outlined in the PRISMA declaration¹¹). We also followed the evaluation criteria of the STROBE statement¹²) for observational and cross-sectional studies as well as the CONSORT checklist¹³) for clinical trials.

RESULTS

Our searches yielded a total of 36 studies on sleep quality in patients with MG published between 1970 and 2014. The number of patients involved in these studies ranged from 9–490. Of the 36 studies, 19 were excluded because they did not meet the inclusion criterion or the eligibility criteria proposed by the STROBE statement or CONSORT checklist. Therefore, a total of 17 studies were included in this review (Fig. 1).

An overview of studies conducted using the criteria of the STROBE statement and CONSORT checklist is presented in Tables 1 and 2.

Thirteen of the 17 studies assessed and analyzed sleep variables using full standard polysomnography (PSG). The studies included in this review are summarized in Table 3.

Table 3. Summary of studies

Authors	Classification	Results	Conclusion
Amino et al. 1998 ¹⁴⁾	Clinical trial	Twelve patients who underwent polysomnography showed obstructive and central sleep apnea.	Sleep apnea is a possible clinical manifestation of MG, and nocturnal dysfunction of both the central and peripheral cholinergic systems may be involved. Patients with longer MG symptom duration tend to have more sleep apnea.
Sonka et al. 1996 ¹⁵⁾	Clinical trial	Typical sleep apnea syndrome (SAS) patterns were observed in 12 subjects, mild saturation undulation without respiratory noises and without heart rate changes in 7 (3 of them also produced the SAS pattern) and irregular nonspecific changes in 3.	There is no relationship between any clinical parameter of MG and the occurrence of nocturnal respiratory disorders. Risk factors for the occurrence of sleep-disordered breathing in MG are similar to those of non-MG population, although the incidence of this condition is higher in MG.
Mennuni et al. 1983 ¹⁶⁾	Observational	Patients with MG exhibited significant differences with respect to increased slow-wave sleep, shorter REM sleep period, and shallower sleep EEG.	The results confirm the presence of a disorder of central nervous system cholinergic activity in patients with MG.
Qiu et al. 2010 ¹⁷⁾	Clinical trial	The prevalences of depression, anxiety, and insomnia in patients with MG were 58.3%, 45.3% and 39.1%, respectively.	Almost half of patients with MG suffer from affective disorders to different degrees.
Stepan-sky et al. 1997 ¹⁸⁾	Cross-sectional	Six of ten MG patients showed central apnea and hypopneas followed by desaturation of oxyhemoglobin during REM sleep.	Patients with MG and sleep apneas have impaired memory function.
Quera-Salva et al. 1992 ¹⁹⁾	Prospective	Patients with abnormally low concentrations of blood gases during the day were at risk for the development of sleep apneas and hypopneas of diaphragmatic origin and oxygen desaturation < 90% during sleep.	Patients with MG, even if treated properly during the day with good functional capacity and activity level, may have abnormal breathing during sleep.
Lapiscina et al. 2011 ²⁰⁾	Retro-spective	A pathological PSQI score, which was observed in 59% of patients, was more common in patients with active disease than those in clinical remission. A relationship was found between PSQI and MG-QOL15 scores in patients with clinically active disease.	Disease severity may be a risk factor specific for MG patients with sleep disorders. The MG-QOL15 and PSQI should be used to estimate the impacts of the disease on sleep and quality of life.
Happe et al. 2004 ²¹⁾	Cross-sectional	Patients with MG showed reduced quality of awakening and sleep efficiency as well as increased number of awakenings and frequency of dream recall.	There is no clear evidence for the model of recovery of awakening or dream recall in patients with MG; the evidence better supports the continuity hypothesis of dreaming. Other factors such as functional status of the brain or anticholinesterase treatment may be important in explaining the dream recall in this patient group.
Nicolle et al. 2005 ²²⁾	Cross-sectional	The prevalence of OSA in MG was 36% compared to an expected prevalence of 15–20% in the general population. When including the presence of daytime sleepiness, the prevalence was 11% compared to 3% in the general population.	Most obstructive events occurred during REM sleep, suggesting oropharyngeal weakness is more important than diaphragmatic weakness.
Siemin-ski et al. 2012 ²³⁾	Cross-sectional	Restless legs syndrome was present in 43.2% of patients with MG and 20% of controls. The study were unable to identify a relationship between the prevalence of restless legs syndrome, the duration and type of therapy MG, other comorbidities, age or sex of patients.	Restless legs syndrome is common in patients with MG.
Ito et al. 2012 ²⁴⁾	Clinical trial	Corticotropin levels were positively correlated with plasma cortisol levels and negatively correlated with anxiety scores/insomnia GHQ-28 in the group prednisolone.	Treatment with low-dose glucocorticoid complements the pituitary–adrenal system and improves the psychological status of patients with MG.
Prudlo et al. 2007 ²⁵⁾	Cross-sectional	Four patients had an AHI > 10/h. There were only a few cases of apneas (central sleep apnea index: $0.19 \pm 0.4/h$). There was no evidence of a causal relationship between clinically stable MG and sleep respiratory disorders in terms of OSA.	The degree of respiratory muscle weakness is not correlated with outcome in MG. The high incidence of central respiratory events during sleep was not confirmed in patients with well-controlled MG.

Table 3. Continued

Authors	Classification	Results	Conclusion
Yeh et al. 2013 ²⁶⁾	Clinical trial	Before double-filtration plasmapheresis, the minimum saturation level of pulse oximetry obtained during the evening session was significantly lower than that during two sessions in the day.	Changes in respiratory function are common in myasthenic patients without clinical respiratory symptoms. Double-filtration plasmapheresis results in minimal improvement of respiratory parameters.
Kassardjian et al. 2012 ²⁷⁾	Prospective	Quantitative Myasthenia Gravis Score improves only after naps longer than 5 min.	Daytime sleep minimizes neuromuscular fatigue in MG patients, especially if they sleep for more than 5 min.
Papazian 1976 ²⁸⁾	Controlled clinical trial	All myasthenic patients exhibited significant disturbances during REM sleep. In the patient who underwent a second polysomnography after prednisone therapy, the pattern of REM sleep returned to normal.	Acetylcholine is the putative brainstem neurotransmitter involved in the maintenance of REM sleep. The findings suggest a central disturbance of the acetylcholine mechanism in MG.
Elsais et al. 2013 ²⁹⁾	Cross-sectional	Among MG patients, 44% (36/82) met the criteria for fatigue versus 22% (90/410) of controls; 21% of patients (17/82) met the criteria for chronic fatigue versus 12% (48/410) of the controls. MG patients had higher total fatigue scores than the controls.	Ethnic Norwegian MG patients have higher levels of fatigue and a higher prevalence of chronic fatigue than controls, even among those in complete remission. The severity of MG is associated with symptoms of autonomic disturbance, which in turn are related to the degrees of fatigue and disability.
Manni et al. 1995 ³⁰⁾	Cross-sectional	All patients had normal blood gases during the day, except for 1 who showed mild hypoxemia. No patients complained of disturbed sleep; 6 patients snored. Five patients showed short and infrequent central apnea, especially during REM sleep, on polysomnography.	In patients with mild generalized MG in a stable functional state, breathing pattern instability during sleep is infrequent; when it occurs, it is generally mild and mainly related to REM sleep.

MG: myasthenia gravis; OSA: obstructive sleep apnea; SAS: sleep apnea syndrome; REM: rapid eyes movement; EEG: electroencephalogram; PSQI: Pittsburgh Sleep Quality Index; MG-QOL 15: Myasthenia Gravis Quality of Life 15 Items; GHQ-28: General Health Questionnaire-28; AHI: apnea/hipopnea index

DISCUSSION

The onset of MG symptoms may be abrupt or insidious, and the disease course is variable. The clinical presentation is characterized by a history of fluctuation between weakness and fatigue in skeletal muscles possibly including the ventilatory muscles. Fatigue is more pronounced at the end of the day and therefore often occurs at home^{31–35)}. Approximately 30% of patients with MG develop some degree of respiratory muscle weakness during the disease course, and 15–20% of these patients will require ventilatory support^{36, 37, 39)}.

The prevalence of sleep disorders in patients with neuromuscular disorders is not well documented in the literature, and symptoms such as daytime sleepiness and fatigue are often attributed to neurological disease^{38, 39)}. Some studies involving patients with MG report poor sleep quality, excessive daytime sleepiness, limb movements during sleep, and the presence of SDB are associated with MG, while others report no such associations; however, the studies that failed to find relationships with MG had small sample sizes and some did not use PSG^{14–20)}.

Sieminski et al.²³⁾ used a questionnaire to determine the prevalence of restless legs syndrome (RLS) in 73 MG patients and 65 healthy controls. They report that 43.2% of patients with MG had RLS compared to 20% of the controls. Therefore, they conclude RLS is more prevalent in patients with MG than the general population. Given that RLS negatively affects the equality of life of patients with MG, there is

a critical need for early diagnosis in this population.

The prevalence of daytime sleepiness is reported to be high in patients with MG, which has been verified by Epworth Sleepiness Scale (ESS). Quera-Salva et al.¹⁹⁾ found that 33% of participants (4/12) reported excessive daytime sleepiness. Nicolle et al.²²⁾ found a pathological ESS score in 25% (21/84) of their study population. Prudlo et al.²⁵⁾ report that 31.5% (6/19) of patients experienced mild or moderate sleepiness (ESS > 8). Furthermore, Martínez-Lapiscina et al.²⁰⁾, Prudlo et al.²⁵⁾, Nicolle et al.²²⁾, and Quera-Salva et al.¹⁹⁾ report that 43%, 70%, 85%, and 100% of patients with MG had generalized muscle weakness, respectively. These findings collectively demonstrate the relationship between stable MG and excessive daytime sleepiness.

Prudlo et al.²⁵⁾ investigated the prevalence of SDB in patients with clinically stable MG. Among the 19 MG patients who underwent PSG, 4 had an apnea-hypopnea index (AHI) > 10/h without central events, similar to findings by other authors.

Quera-Salva et al.¹⁹⁾ observed a high prevalence of SDB in their study of 20 patients with MG, especially during REM sleep. Eleven patients (55%) had an AHI > 5/h during REM sleep. However, the total sleep time AHI scores were >10/h. The authors conclude that patients with MG, including one elderly patient with a high BMI and impaired pulmonary function, are more likely to have SDB.

Manni et al.³⁰⁾ investigated breathing patterns during sleep in 14 patients with MG by using questionnaires, pulmonary function tests, and PSG. The patients exhibited

mild changes in ventilatory patterns, with slight instability in oxyhemoglobin saturation during sleep. Apnea respiratory events were of the hypopnea type and were only observed in 5 patients. However, the number of events per hour was considered within the normal range. This discrepancy with other studies can be attributed to the selection criteria of that study³¹).

Amino et al.¹⁴) used PSG to study physiological variables during sleep in 16 patients with MG. At baseline, 12 patients had either obstructive or central SDB. Nine patients underwent thymectomy, and PSG indicated sleep apneas were abolished in 6 of them. The authors interpreted these findings as evidence that SDB in patients with MG is a nighttime demonstration of the central and peripheral cholinergic symptoms. The main causes of respiratory events during sleep in patients with MG may be changes in activity at the neuromuscular junction. Therefore, thymectomy may reduce the prevalence of SDB in patients with MG.

Yeh et al.²⁶) compared the effects of plasmapheresis on sleep quality as assessed by PSG and a scale of excessive daytime sleepiness in 7 patients with MG. They report a significant improvement in muscle weakness, a reduction in MG 15 score, and improvements in anti-acetylcholine receptor antibody diagnostic testing. However, no significant changes were observed in sleep variables despite clinical improvement²⁷).

In conclusion, for some neuromuscular diseases, it is well established that SDB affects quality of life, compromising health and longevity. Some studies of patients with MG show that patients with MG are associated with poor sleep quality, excessive daytime sleepiness, presence of restless legs syndrome, and a higher incidence of SDB, while other studies do not report such associations. Therefore, given the current inconclusive evidence and limited literature, further study of sleep disturbances in patients with MG is needed.

Future research should use PSG to investigate possible relationships with anthropometric characteristics, pulmonary function, and disease etiology, with particular attention to the time course of disease progression. Such findings may be used to improve sleep disturbances and thus the quality of life of patients with MG.

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