
Sleep Related Conditions with Myasthenia Gravis: Evidence, Causes and Implications

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To cite this article:

Sherifa Ahmed Hamed. Sleep Related Conditions with Myasthenia Gravis: Evidence, Causes and Implications. *Science Journal of Public Health*. Special Issue: Obstructive Sleep Apnea: A Systemic Disease. Vol. 4, No. 2-1, 2016, pp. 6-16. doi: 10.11648/j.sjph.s.2016040201.12

Abstract: Myasthenia gravis (MG) is an autoimmune disease caused mainly by antibodies against skeletal muscle nicotinic acetylcholine receptors (nAChRs) at the postsynaptic membrane resulting in depletion of acetylcholine at the neuromuscular junction (NMJ). Muscle fatigue is the cardinal symptom of MG. Respiratory muscle weakness and breathing problems are manifestations of MG even in mild stages of the disease resulting in significant morbidity and mortality. Also sleep related conditions are among the manifestations of MG which include sleep disordered breathing (SDB) [i.e. central (CSA) and obstructive (OSA) sleep apneas, hypoventilation or hypoxemic syndromes], reduced sleep efficiency and quality, increased number of nocturnal awakenings, excessive daytime sleepiness, reduced rapid eye movement sleep and altered sleep perception and dreaming. On the other hand, sleep abnormalities may result in lack of concentration, cognitive impairments and mood disturbances as depression and anxiety. Central and peripheral mechanisms have been suggested for the association between MG and central nervous system manifestations and sleep abnormalities. Neurologists and sleep medicine professionals should be aware of the associations between OSA/CSA, hypoventilation and other sleep related conditions with MG and consider systematic investigations including polysomnography and ventilatory support. This will reduce morbidity and mortality and improve quality of lives of patients with MG.

Keywords: Myasthenia Gravis, Neuromuscular Diseases, Sleep Disordered Breathing, Obstructive Sleep Apnea, Central Sleep Apnea, Hypoventilation

1. Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease caused mainly by antibodies (Abs) against skeletal muscle nicotinic acetylcholine receptors (nAChRs) at the postsynaptic membrane resulting in depletion of acetylcholine (ACh) at the neuromuscular junction (NMJ) [1]. The cardinal symptoms of MG are muscle fatigue and weakness which peak at the end of the day after repeated exertion and improved by rest [2]. Respiratory muscle weakness and breathing problems are manifestations of MG even in mild stages of the disease [3, 4]. Also sleep related disorders are among the clinical manifestations of MG which include sleep disordered breathing (SDB) [i.e. central sleep apnea (CSA), obstructive sleep apnea (OSA), mixed apnea (OSA and CSA), sleep-related hypoventilation or hypoxemic syndromes] [5-10], poor sleep quality, reduced sleep efficiency, reduced sleep and awakening quality, increased number of nocturnal awakenings, excessive daytime

sleepiness, reduced rapid eye movement sleep (REM sleep) and altered sleep perception and dreaming [6, 8, 11-13] and excessive limb movements during sleep [e.g. restless leg syndrome (RLS)] [14]. Symptoms of SDB and other sleep abnormalities usually develop gradually in patients with MG which often make patients unaware of them. However, they are major causes of morbidity and mortality. Other nervous system manifestations were also reported in some patients with MG as memory difficulties and cognitive impairment [15-18], autonomic dysfunction [19, 20], sensorineural hearing loss [21] and psychiatric disorders [22] which are also related to sleep abnormalities with MG [7]. Several central (e.g. brain ACh deficiency) [9, 17, 19, 23, 24] and peripheral [25, 26] (e.g. respiratory muscle weakness, use of acetylcholine esterase inhibitors (AChE-Is) and weight gain from limited physical activity) mechanisms have been suggested for the association between MG and nervous

system manifestations and sleep related conditions.

This review was written after a detailed search in the PubMed, ISI web of science, EMBASE, SciELO, Scopus and the Cochrane Neuromuscular Disease Group Specialized Register of Controlled Trials from 1970 to 2015 using the following search terms: myasthenia gravis or neuromuscular disease and sleep, sleep quality, sleep apnea, obstructive sleep apnea, central sleep apnea and sleep disordered breathing (SDB). Data from observational, cross-sectional, prospective, retrospective and double-blinded randomized studies, review articles, abstracts, study protocols, letters to the editor and case reports were considered. We also checked the reference lists of the retrieved studies for additional reports. The aim of this review is to summarize the current knowledge on sleep related conditions in patients with MG including evidence and mechanisms. The clinical implications for diagnosis, prevention and treatment approaches were also discussed.

2. General Background About Myasthenia Gravis

MG is a rare disease with a prevalence of 25-125/10⁶ and an incidence of 2.5-10.4/10⁶. MG affects women more than men (3:2) in their 2nd and 3rd decades but after the age of 50, both sexes are equally affected [27, 28]. The diagnosis of MG is made according to the clinical, pharmacologic, electrophysiologic and immunologic criteria. Osserman [29] proposed a clinical classification based on symptom onset, symptom severity, and anatomical distribution of the affected muscle groups and grade patients into the following 5 groups: I (patients with ocular MG), II-A (mild generalized MG), II-B (moderate generalized MG), III (severe MG with respiratory crisis), or IV (the most severe form and develops at least 2 years after the patient has been in group I and II with poor response to therapy). Diurnal fatigability after exercise and restoration of strength by rest are the clinical hallmarks of patients with MG and most patients show normal muscle power after nocturnal sleep. The ocular muscles (grade I) are initially involved in about 2/3 of patients with MG and the disease remains confined to the ocular muscles in 10-15% of patients while 70-85% of patients develop generalized weakness (grades II-A and II-B). Dysphagia, dysarthria, and dysphonia are common manifestations of MG [2]. Respiratory or breathing abnormalities are also common manifestations of MG [3, 4].

Diagnostically, muscle weakness improves with intravenous administration of edrophonium (tensilon) [a fast-acting acetylcholinesterase inhibitor (AChE-I)]. Its action starts within 30 seconds and lasts for about 5 minutes [30]. Ice test is a bed side test for diagnosing MG. It is done by applying ice for 2-5 minutes to the fatigued muscles (e.g. eyelids where ptosis is present). This test has a sensitivity and specificity of 76.9% and 98.3%, respectively for the identification of MG. The basis of this test is the fact that AChE is inhibited at lower temperature. The test is

considered positive if there is a ≥ 2 mm raise in the eyelid after the ice is removed [31]. On electrophysiological examination, most patients exhibit decremental electromyographic response on repetitive supramaximal stimulation of the motor nerves and increased jitter and neuromuscular blocking in single fiber electromyography [EMG]. Jitter is the abnormal variation in the time interval between action potentials of adjacent muscle fibers in the same motor unit. Blocking is the failure of nerve impulses to elicit action potentials in adjacent muscle fibers of the same motor unit [32]. Approximately 80–90% of patients with generalized MG and 30-50% of patients with ocular MG are seropositive for muscle nAChRs Abs [1]. Antibodies to muscle-specific kinase (MuSK) have been identified in about 30-40% of patients with classic manifestations of MG but seronegative for muscle nAChRs Abs. Anti-MuSK Abs has been thought to alter clustering of AChRs during NMJ formation [33]. MG positive to anti-MuSK Abs has distinct patterns of weakness compared to MG positive to nAChR Abs. The former usually has weakness of facio-pharyngeal, neck extensor, respiratory and proximal muscles without ocular muscle weakness and atrophy of the tongue and face [34]. In adults with MG, the thymus gland is abnormal in $\geq 90\%$ [35] (figure 1).

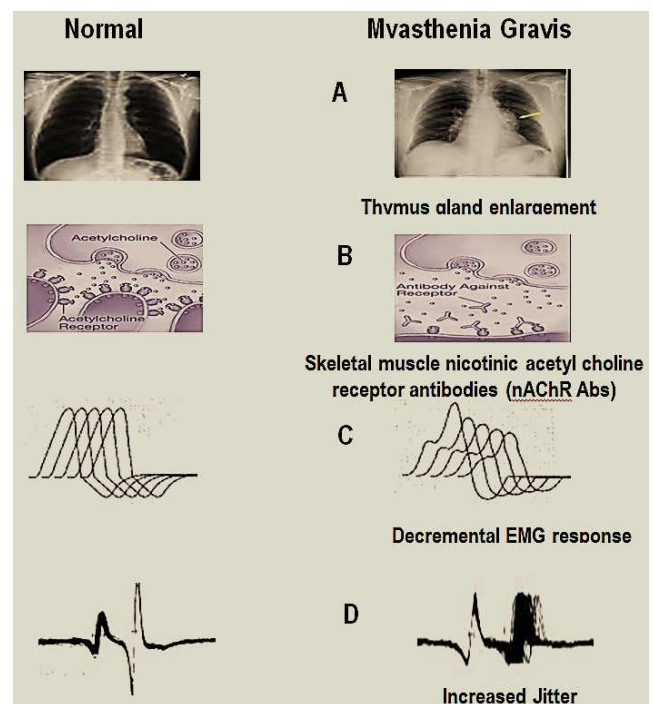


Figure 1. Pathophysiology of MG: Immunity related to the thymus gland (hyperplasia or thymoma) (A) produces skeletal muscle nicotinic acetyl choline receptor antibodies (nAChR Abs) (B) which result in skeletal muscle fatigue and weakness, decremental EMG response on supramaximal nerve stimulation of the weak muscle (C) and increased jitter and neuromuscular blocking in single fiber electromyography (D).

The usual onset of MG is gradual. Remissions with MG can occur early during the first 3 years of the disease, however, long and complete remissions are very rare [2]. MG has a variable clinical course that may be exacerbated by

stress including infection, exertion or various drugs that may lead to myasthenic crisis (manifested by severe weakness, respiratory distress/arrest, poor cough, dysphagia, inability to handle oral secretions, cyanosis, increased pulse and blood pressure and diaphoresis). Complications as myasthenic crisis and acute oropharyngeal dysfunction followed by the rapid onset of respiratory failure occur in 12-16% of patients [2, 3].

The current treatment for MG due to nAChR Abs include AChE-Is (as pyridostigmine) [36], immunopharmacologic drugs [37, 38] and thymectomy [39] while for anti-MuSKR-Ab MG, the therapeutic response is better with plasma exchange and immunosuppressive therapy but not with AChE-Is [10].

3. Evidence of Respiratory Muscle Weakness and Sleep Abnormalities in Patients with Myasthenia Gravis

3.1. Normal Breathing and Muscle Activity During Sleep

In general, normally during sleep, there is increase in the upper airway resistance, reduction in chemosensitivity and loss of the wakefulness drive of breathing resulting in a fall in ventilation. At sleep onset (transition of electroencephalography or EEG shift from alpha to theta activity) and during nonrapid eye movement sleep [NREM], the upper airway resistance increases abruptly due to reduced activity of the pharyngeal dilator muscles. The increase in phasic diaphragmatic and intercostal electromyographic (EMG) activity in NREM sleep (following the transient fall at sleep onset) reflects the rise in respiratory workload due to increased upper airway resistance. In contrast, ventilation falls abruptly and is associated with a more rapid, shallow and regular breathing pattern [40], resulting in a rise in the partial pressure of carbon dioxide (PCO_2). The rise in genioglossus activity during NREM sleep, after the initial fall at sleep onset may be important in maintaining airway patency. Once sleep becomes established and with progression of sleep (slow wave sleep with predominance of delta EEG activity), there is a further progressive rise in upper airway resistance while ventilation shows only a slight further decline [41]. During rapid eye movement (REM) sleep, there is greater inhibition of the upper airway musculature leading to pharyngeal narrowing during eye movements. Also the ribcage and accessory breathing muscles are suppressed, particularly during bursts of eye movements (i.e there is a shift predominantly from ribcage to diaphragmatic breathing), and breathing is more irregular, rapid and shallow, with a further fall in ventilation [42].

3.2. Respiratory Muscle Weakness in Patients with MG (table 2)

During the initial disease phase, only 1–4% of patients have dysfunction of the respiratory muscles (which include: diaphragm, accessory muscles, upper airway muscles and

abdominal muscles that stabilize the chest); however, in the later stages, 30–40% of patients develop respiratory muscle weakness, abnormal breathing pattern and blunted ventilatory responses and 15–20% of these patients will require ventilatory support [3, 4]. Rarely, respiratory failure in patients with MG may occur as a result of upper airway obstruction. Schmidt-Nowara et al. [43] reported paroxysmal dyspnea and stridor in a patient with MG due to weakness of vocal cord abductors that improved with AChE-Is. In patients with mild and moderate MG with no respiratory symptoms, several authors reported abnormal pulmonary function tests and measurements of respiratory muscle strength particularly during REM sleep which improved with AChE-Is [6, 44, 45].

Table 1. Sleep related conditions with MG and their consequences.

Excessive daytime sleepiness
Reduced sleep and awakening quality
Reduced sleep efficiency
Reduced REM sleep
Increased number of nocturnal awakenings
Morning drowsiness
Morning headaches
Altered sleep perception and dreaming
Increased dream recall frequency
Increased tactile sensations during dreaming
Dreams are less often visually
Restless leg syndrome
Sleep disordered breathing which include obstructive sleep apnea (OSA), central sleep apnea (CSA), mixed apneas, hypopneas and hypoventilation or hypoxemic syndrome
Lack of concentration, memory and cognitive deficits
Psychiatric manifestations as depression and anxiety

3.3. Sleep Related Conditions with MG (table 1 and 2)

Many observational, cross-sectional and clinical studies reported that patients with MG may suffer from excessive daytime sleepiness [6, 9, 11, 12, 45], reduced sleep and awakening quality, reduced sleep efficiency, reduced REM-sleep, increased number of nocturnal awakenings, microarousals, poor sleep quality index scores [13], morning drowsiness, headaches [11, 13], altered sleep perception and dreaming, increased dream recall frequency, increased tactile sensations during dreaming and dreamed less often visually [11] and restless leg syndrome (RLS) [14]. Excessive daytime sleepiness was reported in 25% (21/84) [9] and 31.5% (6/19) [12] of patients with MG. Studies reported no relationship between stable MG and excessive daytime sleepiness [6, 9, 12] and lack of effect of plasmapheresis treatment on polysomnographic abnormalities despite improved clinical weakness and decreased MG score and AChR Abs concentration [46]. Also RLS was not found to correlate with the disease duration, type of therapy of MG, age, sex or associated comorbidities with MG [14].

Table 2. Results of studies for evaluation of respiratory muscles and sleep related conditions in patients with MG.

References	Population studied and type of studies	Findings in patients with MG
Papazian [52]	10 patients	10 patients had a significant disturbance in REM sleep cycles. In a patient who was retested after clinically successful prednisone therapy, the REM sleep pattern became normal.
Mennuni et al. [57]	9 patients	Slow wave sleep was better represented; average REM period length was shorter and electroencephalography (EEG) was unstable and tended toward lightening of sleep.
Mier-Jedrzejowicz et al. [44]	17 patients with generalized mild-to-moderate MG	94.12% (n=16) had reduced maximal static expiratory and inspiratory mouth pressures. 70.59% (n=12) had abnormal vital capacity (VC). 47.06% (n=8) had reduced transdiaphragmatic pressure recorded during maximal sniffs (sniff Pdi) and 17.65 (n=3) had reduced bilateral phrenic nerve stimulation at 1 Hz (twitch Pdi). There was no relationship between the grade of MG or the severity of dyspnea and any of the measurements of respiratory muscle strength. After the administration of tensilon, there was a significant increase in maximal static expiratory and inspiratory mouth pressures and in sniff Pdi.
Shintani et al. [5]	10 clinically well-controlled MG	60% (n=6) of patients [with average age: 47.8 years and average duration of illness: 6.2 years] had OSA and CSA appeared for periods >10 seconds and >30 times in one night. Their mean Apnea Index (AI) was 14.6, the duration of mean apnea was 23.4 seconds and the average frequency was 99.0 times. 40% of patients [with average age: 30.8 years and average duration of illness: 0.9 years] had no apneas. The longer duration of illness was a risk for the occurrence of sleep apnea syndrome.
Quera-Salva et al. [6]	20 patients with a mean age of 40 years	All patients (n=20) had evidence of daytime diaphragmatic weakness as demonstrated by transdiaphragmatic pressure measurements, independent of the degree of autonomy and functional capacity and activity level. 55% (11/20) of patients had sleep apnea. Risk factors for the development of diaphragmatic sleep apneas and hypopneas, and oxygen desaturation of less than 90% during sleep were older age, higher body mass index, abnormal total lung capacity and abnormal daytime blood gas concentrations.
Spinelli et al. [45]	12 patients with moderate generalized (IIb) MG before and after an orally administered therapeutic dose (120 mg) of mestinon	Before mestinon, patients had slight decrease in vital capacity, and normal total lung capacity and forced expiratory ventilation to vital capacity ratio (FEV1/VC ratio). Respiratory muscle weakness was evidenced by the marked decrease in maximal inspiratory (MIP) and expiratory (MEP) pressures, the more rapid and shallower breathing (RSB): lower tidal volume (VT), inspiratory time (TI), expiratory time (TE), and greater respiratory frequency (f); mean inspiratory flow (VT/TI) and mouth occlusion pressure (P0.1) were slightly supernormal, whereas both surface electromyographic activity of the diaphragm (EMGd) and intercostal (EMGint) muscles were significantly higher in patients. During hypercapnic rebreathing, ventilation (VE), VT, VT/TI, P0.1 and EMGd response slopes to increasing PCO ₂ were found to be lower, whereas EMGint response slope was normal. At 60 mm Hg of PCO ₂ in the two groups (before and after mestinon), the difference in terms of breathing pattern, P0.1, and EMGd were similar to that observed during room-air breathing. After mestinon, VC, MIP, and MEP were significantly increased, whereas spontaneous breathing remained unchanged.
Manni et al. [51]	14 patients with a stable functional state	All patients (n=14) had normal daytime blood-gas values, except one who showed mild hypoxemia. No patient complained of disturbed sleep. Six patients reported snoring. 5 patients had short and infrequent central apneas mainly during REM sleep, together with a drop in HbSaO ₂ levels >5% of the baseline wakefulness value. REM sleep was the time of highest breathing vulnerability during sleep.
Sonka et al. [53]	28 treated patients with MG ocular form = 12 cases, mild generalized form = 5 cases, medium generalized form = 10	42.86% (12/28) had typical sleep apnea syndrome patterns. 25% (7/28) had mild saturation undulation without respiratory noises and without heart rate changes, of them 3 (42.86% or 3/7) had typical sleep apnea syndrome patterns. 10.71% (3/28) had irregular nonspecific

References	Population studied and type of studies	Findings in patients with MG
	cases and free of symptoms after thymectomy = 1 case	changes. The average vital capacity in patients with sleep apnea syndrome and with MESAM4 abnormality was higher compared to those without MESAM4 abnormality. The average of oxygen saturation minima in patients with sleep apnea syndrome was significantly lower in patients without MESAM4 abnormality. The risk factors of the occurrence of sleep respiratory disturbances in MG were similar to those of the non-myasthenia population although the incidence of this condition in MG was higher.
Stepansky et al. [7]	19 patients	60% had central type of sleep apneas and hypopneas with resulting oxygen desaturations occurring during REM-sleep, but no decrease of REM sleep, normal vigilance performance but decreased memory function. Patients with sleep apnea had an impaired memory function.
Amino et al. [8]	16 clinically well controlled patients	75% (12/16) had OSA/CSA [mean age: 42.4±16.4 years, mean duration of MG: 7.4±6.96 years]. Sleep apnea was not detected in 4 patients [mean age: 30.8±10.71 years and mean duration: 0.9±0.65 years]. Patients with a longer duration of MG tended to have more SA. Sleep apnea resolved in 66.67% of patients who did thymectomy.
Happe et al. [11]	17 patients [mean age 49.5±13.6 years]	Reduced subjective sleep and awakening quality and sleep efficiency were reduced, increased number of nocturnal awakenings as well as dream recall frequency. Patients reported more often body-related and tactile sensations during dreaming and dreamed less often visually
Nicolle et al. [9]	86 patients	25% (21/84) had excessive daytime sleepiness. The prevalence of OSA was 36% compared to an expected prevalence of 15 to 20% in the general population. When including the presence of daytime sleepiness (OSA syndrome), the prevalence was 11% compared to 3% in the general population.
Prudlo et al. [12]	19 clinically stable MG [mean disease duration of 9.7 years]	31.55 (6/19) had excessive daytime sleepiness. 21.05% (n=4) had OSA . 15.79% (n=3) had only a few central apneas. No identified relationship between maximum inspiratory pressure and OSA No evidence for a causal relationship between medically stable MG and SDB in terms of OSA. The extent of respiratory muscle weakness failed to correlate with OSA.
Yeh et al. [46]	7 patients At baseline and 1 day after completion of the last session of plasmapheresis.	Despite improvement of myasthenic weakness in all patients with a median decrease in MG score of 2 points and a median clearance of 43.3% of AChR Abs. no significant change in polysomnographic parameters were detected, except for a trend toward shorter duration of the longest apnea period following the treatment.
Qiu et al. [65]	161 patients	The prevalence of depression, anxiety and insomnia was 58.3%, 45.3% and 39.1% respectively. The correlation factors with significant influences on MG were as follows: depression with age, physical weakness, score of MG, life scale grading; anxiety with experience-sharing; score of MG with insomnia, age, dyspnea, thymoma, physical status at 1 month post-operation and prednisone dose.
Ito et al. [67]	47 patients	The anxiety and depression scores from the 28-item general health questionnaire (GHQ-28) in the patients treated with prednisolone (n=10) were lower than those who were not treated with prednisolone (n=29). Corticotropin levels were negatively correlated with anxiety/insomnia scores from the GHQ-28 in the patients treated with prednisolone. The authors concluded that low-dose glucocorticoids treatment complemented the pituitary-adrenocortical system and improved the psychological state in MG patients.
Martínez-Lapiscina et al. [13]	54 clinically stable patients	A pathological Pittsburgh Sleep Quality Index (PSQI) score, which was observed in 59% of patients, was increased in subjects with active disease compared with patients in clinical remission. In patients with clinically active disease, the authors found a relationship between PSQI and 15-Item-Quality-Of-Life Instrument for MG (MG-QOL15) scores.
Naseer et al. [85]	a 73-year-old male with ocular MG	Therapeutic use of continuous positive airway pressure (CPAP) resulted improvement of

References	Population studied and type of studies	Findings in patients with MG
		not only SDB but also ocular MG.
Sieminski et al. [14]	73 patients	Restless leg syndrome (RLS) was present in 43.2% of the MG patients and in 20% of the controls. No relationships were observed between the prevalence of RLS and the duration and type of MG therapy, other comorbidities and age or sex of the patients. Patients with MG more frequently reported daytime sleepiness. RLS symptoms represented the most disturbing health problem in 9.4% of the RLS-positive MG patients and RLS was as problematic as other diseases in 46.9% of them.
Kassardjian et al. [80]	8 patients with mild to moderate MG	Results showed that The Quantitative Myasthenia Gravis Score (QMGS) improves only after naps where patients slept more than 5 minutes but not where patients did not sleep or slept less than 5 minutes.
Yeh et al. [79]	18 patients This was a prospective study done before and after double filtration plasmapheresis (DFPP) treatment	Mean MG score was markedly lower after DFPP treatment than before treatment. Before DFPP, the minimum pulse oximetric saturation (SpO ₂) level obtained during the night session was significantly lower than the levels obtained during the two daytime sessions. A similar phenomenon was noted for maximum transcutaneous carbon dioxide tension (PtcCO ₂). After DFPP treatment, the maximum and mean PtcCO ₂ levels were significantly higher in the morning than in the afternoon. Of all the respiratory function parameters measured, only minimum SpO ₂ levels obtained during morning sessions before DFPP treatment differed significantly from those obtained after DFPP treatment. Overall, however, minimum SpO ₂ levels as well as mean and maximum PtcCO ₂ levels improved significantly during sleep after DFPP.
Ji et al. [68]	2 patients	Continuous positive airway pressure (CPAP) therapy successfully improved rare occurrence of paradoxical weakness in some patients with MG.
MG, myasthenia gravis; SDB, sleep disordered breathing; OSA, obstructive sleep apnea Grading of MG was done according to Osserman classification [29]		

3.4. Sleep Apneas in Patients with MG (table 2)

Studies reported that the majority of patients with MG experience sleep-related breathing disorder or sleep-disordered breathing (SDB) even if well controlled on medical treatment [5-10]. SDB include central sleep apnea (CSA), obstructive sleep apnea (OSA), mixed apneas (OSA and CSA), hypopneas and hypoventilation or hypoxemic syndromes. Both central (CSA) and obstructive (OSA) types of sleep apneas and hypopneas may occur with MG. CSA describes a group of conditions in which cessations in air flow occur without respiratory effort [47]. In contrast, with OSA, there is ongoing respiratory effort during the respiratory events. With repeated episodes of OSA, the cessation of breathing and/or hypopnea for at least 10 seconds and the reduction of airflow for at least 30% result in a 4% drop in blood oxygen saturation level [48]. CSA was reported in up to 60% of patients with MG [7] compared to 0.3%-7.8% of general population [49, 50]. The prevalence of OSA in patients with MG was estimated to be 36% [9] compared to an expected prevalence of 15 to 20% in the general population. If daytime sleepiness was included, the prevalence of OSA was estimated to be 11% compared to 3% in the general population [49, 50]. Sleep apnea syndrome was reported in 21.05% (4/19) [12], 38.46% (5/13) [51], 55% (11/20) [6], 60% (6/10) [5] and 75% (12/16) [8] of patients

with MG who were well controlled on medical treatment particularly during REM sleep. Some studies reported that variations in disease state and antibody types of MG may also influence the severity of SDB and improvement of sleep apneas (e.g. Anti-MuSKR-Abs is initially associated with OSA and hypoventilation) [34] and REM sleep abnormalities occurred with proper treatment of MG [52]. However, others reported no relationship between sleep apnea syndrome and severity of MG or respiratory muscle weakness in patients with clinically stable MG [12]. Few studies reported no relationship between any clinical parameter of MG and the occurrence of nocturnal respiratory disturbances and suggested that the risk factors of the occurrence of sleep respiratory disturbances in MG are similar to those of the non-myasthenia population although the incidence of this condition in MG is higher [53]. While others reported that the older age, higher body mass index (BMI), the longer duration of illness, diaphragmatic weakness, abnormal total lung capacity, restrictive pulmonary syndrome, daytime alveolar hypoventilation and abnormal daytime blood gas concentrations [5, 6, 8, 54] are common risk factors for the development of sleep apnea syndrome in patients with MG.

4. The Possible Mechanisms of Sleep Related Conditions in Patients with MG

The combination of central and peripheral mechanisms has been suggested as causes of nervous system manifestations and sleep related conditions with MG.

The generalized cholinergic deficiency hypothesis has been suggested by some authors as a cause of sleep and other central nervous system abnormalities with MG. This hypothesis raises the suggestion of involvement of the cholinergic nervous systems and its pathways by well-known (e.g. neuronal nAChR Abs) [9, 17, 19, 23, 24, 55] and others not well-known immune mediated processes (e.g. tumor immunology or non-specific autoimmunity or paraneoplastic manifestations) [56] as causes of central nervous system manifestations with MG. This suggestion is also supported by the followings: 1) Reduction of REM sleep [57] and the increase of oropharyngeal, intercostal and diaphragmatic muscle weakness [57], the predominance of CSA/OSA, hypopnea and hypoxia [57] and increased dream recall frequency [11] during REM sleep. ACh is the putative brainstem transmitter substance involved in the maintenance of REM sleep [58]. In general, sleep apnea (whether CSA or OSA) occurs frequently during REM sleep [52, 57]. This may be related to the important role of the central cholinergic system in sleep/wake rhythms and in the regulation of REM sleep, sleep perception and dreaming [58]. While magnification of OSA during REM sleep is due to the natural loss of intercostal muscle tone during that period [58]. 2) Detection of AChR Abs in the cerebrospinal fluid in patients with MG [59-62]. 3) The presence of structural identities between different nAChRs subunits (i.e. muscular and neuronal subunits) with the possibility of cross-reactivity between anti-nAChR $\alpha 1$ antibodies and other nAChR subunits [24, 63].

Others suggested that central nervous system manifestations and sleep related conditions in patients with MG are caused by peripheral mechanisms which include respiratory and oropharyngeal muscle weakness, adverse effect of AChE-Is and psychiatric manifestations. This suggestion is also supported by the followings: 1) OSA associated with MG appears to be due to reduced pharyngeal dilator muscle activity with bulbar fatigue or weakness and impairment of muscles of the upper airway by the disease process. This causes the diaphragm and intercostal muscles unable to overcome changes in airway resistance. When the patient exerts an increased effort to inspire against the occluded airway, the situation becomes worse due to the creation of more negative airway pressure. Occlusion continues until arousal occurs and the resulting increased tone of the pharyngeal muscles reopens the airway. It was found that in patients with OSA, there was an increased propensity for CSA [64]. 2) Apneic or hypopnic events are usually associated with micro-arousals and sleep disruption. 3) A strong relationship between the sleep apneas (particularly in

presence of long apneic events of ≥ 2 minutes and associated oxygen desaturation) was found in patients with MG and periods of confusion, the inability to concentrate, shortened attention span throughout the waking hours and short-term memory impairment [7]. 4) High frequencies of depression (58.3%), anxiety (45.3%) and insomnia (39.1%) were reported in patients with MG [65]. It has been suggested that sleep fragmentation, lack of REM sleep and severely disrupted sleep patterns may result in personality changes, irritability, anxiety, depression, lack of concentration and memory deficits in patients with MG [7, 66]. Ito et al. [67] reported relationships between pituitary hormonal stress axis, the immune system and the psychological abnormalities (e.g. anxiety and insomnia) in patients with MG. 5) Some authors highlighted the possible role of sleep disturbances such as partial arousal, sleep fragmentation, sleep deprivation and disturbed restorative sleep in developing a paradoxical weakness in MG (i.e. fatigability and weakness in the morning) [68]. Others speculate that paradoxical weakness with MG arises from muscular loading, metabolic or mechanical aspects of nocturnal burdens and non-restorative sleep in MG. Some hypothesize that specific phenomenon of paradoxical weakness in MG is confined only to MG with OSA due to its role in immune-modulation and increasing the risk of autoimmune disease by T-cell mediated manner. Sleep deprivation is also associated with reductions in immune response [69].

5. Clinical Implication

Neurologists and sleep medicine professionals should be aware of the associations between MG, respiratory failure and SDB and other sleep abnormalities encountered in patients with MG. This is important not only for determining prognosis but also for treating patients.

For patients with neuromuscular disorders including MG, some authors suggested that patients, even when stable and controlled on treatment, should be monitored during sleep at least once per year [using a sleep questionnaire, baseline respiratory function tests and standard nocturnal polysomnography] and more if symptomatic (e.g. appearance of nocturnal symptoms as snoring, witnessed apneas, choking or gasping, insomnia, arousals and diaphoresis and/or daytime symptoms as excessive daytime sleepiness, memory impairment, personality changes, morning headaches, depression and nocturia; or frequent upper respiratory infection or indication of daytime CO₂ retention) [13, 70]. Bye et al. [71] reported that simple measurements of vital capacity (VC) in the erect and supine positions and arterial blood gas tensions when the patient is awake have been found to provide a useful initial guide to the degree of respiratory failure occurring during sleep in patients with neuromuscular disorders.

For patients with neuromuscular disorders including MG, some considerations have to be undertaken before and during preparing patients for surgery (e.g. thymectomy). Some patients with MG are very sensitive to the effects of

respiratory depressants, such as opioids, barbiturates and benzodiazepines, thus they should be avoided as pre-anesthetic medications [72]. Inhalational anesthetics as isoflurane may be safely used in patients with MG as it promotes some degree of muscle relaxation and induces 30% to 50% neuromuscular block. Thiopental is better avoided for patients with MG as it may depress peripheral synapses and NMJ [73]. Nitrous oxide may also be used in patients with MG without worsening of the disease [74]. Epidural catheter using bupivacaine may be safely used in patients with MG as they allow more fractional local anesthetic doses, less hemodynamic reperfusion, lower anesthetic doses and allow completion of the surgical procedure [75, 76]. Some patients with MG are very sensitive to the effects of vecuronium, thus the intermediate or short action drugs as atracurium, rocuronium and mivacurium may be safely used as non-depolarizing neuromuscular blockers. Succinylcholine is better avoided in patients with MG due to the unpredictable response from it (as resistance, prolonged effect or unexpected responses) [72, 77, 78].

In some patients with MG, sleep related conditions do not improve despite of improvement of muscle weakness, thus resolution of SDB, nocturnal hypoventilation, disturbance of REM sleep and daytime symptoms have to be considered among the treatment approaches for patients with MG [10, 46, 79]. Treatment must be adjusted to the severity of the problem during sleep. Kassardjian et al. [80] reported that daytime napping for ≥ 5 minutes resulted in improvement of Quantitative MG Score (QMGs). Therapeutic approaches may also include noninvasive support of breathing during sleep. Nocturnal nasal intermittent [81] and long-term [82] positive pressure ventilation have been identified as effective means of stabilizing the oropharyngeal airway, improving respiratory drive during sleep and awake states, improving arousal responses to abnormal blood gases, normalizing awake blood gases, improving arterial oxygen (PaO_2) and carbon dioxide (PaCO_2) tensions, inspiratory muscle strength, spontaneous breathing during sleep, oxygen desaturation during NREM sleep, arterial oxygen saturation during NREM sleep and reduce CO_2 retention in REM and NREM sleep states [83, 84]. Some reported that the use of continuous positive airway pressure (CPAP) resulted in improvement of not only SDB but also ocular MG [85] and fatigability and weakness in the morning [paradoxical weakness (PW)] associated with OSA [68].

Future longitudinal research studies are need to investigate the possible relationship between sleep states and pulmonary function with the time course of disease progression and to elucidate the exact role of the central cholinergic system in the pathogenesis of central nervous system abnormalities including sleep disorders in patients with MG.

Conflict of Interests

The authors declare that they have no competing interests. Authors did not receive fund for this work and all were authors' responsibility.

Abbreviations

MG, myasthenia gravis; NMJ, neuromuscular junction; nAChRs, nicotinic acetylcholine receptors; ACh, acetylcholine; Abs, antibodies; AChE, acetylcholinesterase; AChE-Is, acetylcholinesterase inhibitors; Anti-MuSK Abs, muscle-specific kinase antibodies; SDB, sleep disordered breathing; CSA, central sleep apnea; OSA, obstructive sleep apnea; REM, rapid eye movement; NREM, non-rapid eye movement; CPAP, continuous positive airway pressure

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