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Treatment Approaches to Myasthenia Gravis and Obstructive Sleep Apnea: Case Report

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Abstract

Myasthenia gravis (MG) is a chronic autoimmune disease characterized by progressive weakness and skeletal muscle fatigue due to the destruction of acetylcholine receptors, causing an abnormality in the synaptic junction between innervation and muscle fibers. The treatment of patients with MG and obstructive sleep apnea (OSA) is positive pressure in the airway; however, the lack of adherence to the protocol can lead to increased morbidity. A known alternative treatment for OSA is the mandibular advancement device (MAD). The objective of the present report is to describe an emblematic case of a 50-year-old male patient with MG with sleep complaints and documented OSA, and his response to different treatment approaches.

Keywords
- mandibular advancement device
- myasthenia gravis
- obstructive sleep apnea

Introduction

Myasthenia gravis (MG) is a chronic autoimmune disease characterized by progressive weakness and skeletal muscle fatigue due to the destruction of acetylcholine receptors, causing an abnormality in the synaptic junction between innervation and muscle fibers.[1] The severity of the disease depends on the muscular groups involved, ranging from mild cases with purely ocular symptoms to severe cases with generalized muscular weakness, including respiratory failure, causing obstructive sleep apnea (OSA) in more than 30% of the patients.[2–5] In some cases, patients also present with hypoventilation, of different degrees of severity.[6]

The relevance of an association with sleep-disordered breathing (SDB) is based on the early observation that MG patients frequently died of respiratory failure in the early morning hours, before the intervention of intensive care medicine. Indeed, several previous reports document an increased prevalence of SDB in patients with MG.[3] The most common type of SDB is OSA, which is thought to be particularly prevalent in patients with neuromuscular diseases. The pathophysiology of OSA is complex and involves a combination of factors, including muscular weakness, narrowing of the upper airway, and decreased muscle tone during sleep. These factors can lead to recurrent episodes of shallow or interrupted breathing during sleep, which can result in decreased oxygen levels in the blood. This can have serious consequences for patients, such as increased risk of heart disease, stroke, and death.[2,3]The presence of sleep

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disorders is not always obvious or observed, and the patients often attribute the symptoms of daytime sleepiness and fatigue to the neurological disease. Obstructive sleep apnea compromises the breathing of patients with neuromuscular diseases, progressively worsening cardiopulmonary function, causing morbidity, and decreasing the quality of life.[7–9] The recommendation for patients with MG who are treated for OSA is the use of noninvasive mechanical ventilation with two levels of positive airway pressure ventilation.[2,3,10] The gold standard of the OSA and/or hypoventilation treatment in MG is bilevel positive airway pressure (BiPAP).[10] However, there are some patients who do not adapt to the treatment and therefore need to search for treatment alternatives.[11–13]

A retrospective study[13] of more than 2 thousand patients using a mandibular advancement device (MAD) with an 80% success rate demonstrates an innovative approach to the use of this therapy for OSA patients. The MAD is also prescribed as an alternative for OSA patients, in particular for those who do not adapt to positive pressure and have OSA exclusively.[2,10,11]

The objective of the present report is to describe a clinical case of treatment with intraoral MAD in an individual with MG.

Clinical Case

A 50-year-old male patient diagnosed with MG was referred to the neuromuscular outpatient clinic at Universidade Federal de São Paulo (Unifesp, in Portuguese), in the city of São Paulo, Brazil. He complained of weakness in the arms and in the right leg, with difficulty in carrying weight and walking, in addition to complaints of tiredness and breathing difficulty. He also complained of impaired chewing and a crooked mouth while talking, feeling numb, neck pain, and drooping eyelids, which worsened in the afternoon. Under treatment, the symptoms improved, but did not stop. The medications prescribed were pyridostigmine (120 mg/day), azathioprine (50 mg/day), prednisone (50 mg/day), folate, and calcium.[14]

The patient presented to the clinic with a polysomnography (PSG) exam and a diagnosis of OSA from his local city. He complained of loud snoring, and reported breathing pauses and daytime sleepiness. He was then referred for BiPAP treatment, with inspiratory positive airway pressure (IPAP) ranging from 14 cmH2O to 15 cmH2O and expiratory positive airway pressure (EPAP) ranging from 8 cmH2O to 9 cmH2O, with oronasal mask and heated humidifier. He used BiPAP for 3 years with a mean adherence of 6 hours. After this 3-year period, he started having problems with BiPAP adherence, which dropped to 2 hours in the next 1.5 year, coming to a complete dropout after another year. Complaints of BiPAP difficulty included mask fitting. He dropped treatment with BiPAP after cataract surgery, reporting more discomfort. The BiPAP report revealed not only the adherence in hours, but also showed apnea-hypopnea resolution, with a maximum apnea-hypopnea index (AHI) of 3 obstructive events per hour per night, and 89% of hemoglobin oxygen saturation (SpO_2).

The patient was then referred to the dental clinic due to lack of adherence to the BiPAP, again complaining of loud snoring.

Upon arriving at the dental clinic, the patient had no complaints related to temporomandibular disorders (TMDs). He brought a recent PSG exam, with an AHI of 6.6 events per hour, Respiratory Disturbance Index (RDI) of 13.8 events per hour, total sleep time (TST) of 335.5 minutes, minimum SpO2 of 89%, 0.2 minute of SpO2 lower than 90%, and an oxygen desaturation index of 18.3 events per hour during rapid eye movement (REM), sleep and of 3.5 events per hour during non- rapid eye movement (NREM) sleep. The end-tidal carbon dioxide ($P_{ET}CO2$) was of 39 mmHg during wakefulness, of 38 mmHg during REM, and of 40 mmHg during REM sleep, with a peak of 47 mmHg during the night. His sleep was fragmented, showing an arousal index of 25.9 events per hour, low sleep efficiency, of 72.3%, 11.2% of N1, 35.2% of N2, 39.9% of N3, and 13.7% of REM sleep. Loud and frequent snoring was reported. The overall PSG results and the medical evaluation suggested symptomatic mild OSA and absence of hypoventilation during sleep (►**Table 1**).

The dental evaluation showed that the patient presented four missing permanent teeth, being one in the maxillary arch and three in the mandibular arch, and a well-balanced face.

There were complaints of loud snoring, restless sleep, and two awakenings at night, with preferably lateral decubitus. The average sleep duration was of 6 hours per night. A complete orthodontic documentation was requested before the initiation of the treatment. The lateral teleradiograph showed parallelism between the bone bases, proportionality of the maxillomandibular complex, and well-positioned apical bases, and panoramic radiography showed extensive restorations, dental elements with endodontic treatments, and root pins supporting prosthetic crowns.

The device was placed with 50% of mandibular advancement, progressive advances of 1 mm were made fortnightly, and, until symptoms improved, the maximum advancement was of 11 mm. There were no muscle complaints with the use of the device, nor pain on palpation tests in the muscles and the temporomandibular joint. The patient reported significant improvement in daytime symptoms, including fatigue. He also reported using the device throughout the night, on an average of 7.5 hours, which suggests good adherence to the MAD treatment.

After one year of follow-up, the patient had no complaints related to TMD, and there was a sustained report of improvement in snoring, his main complaint, but also in daytime symptoms, with better quality of life. The patient did not change his drug treatment, nor did he start any other physical treatment during one year of MAD treatment.

The PSG with MAD showed an AHI of 4.3 events per hour, an RDI of 13.6 events per hour , and a TST of 308.0 minutes, with mild and infrequent snoring, arousal index of 16.6 events per hour, minimum SpO2 of 89%, 0.1 minute of SpO2 lower than 90%, N3 of 29.4%, REM of 14.9%, and sleep efficiency of 74% (►**Table 1**).

Table 1 Polysomnography 1 (PSG1) results from baseline (before starting the myasthenia treatment), PSG2 (for BiPAP titration), PSG3 (1 year after dropping BiPAP, under neurological treatment), and PSG 4 (under MAD treatment).

	PSG1	PSG2	PSG3	PSG4
Sleep efficiency (%)	67	86.2	72.3	74
Total sleep time (TST; in minutes)	264.5	347.5	335.5	308
N3 sleep (%)	2.7	31.1	39.9	29.4
Rapid eye movement (REM) sleep (%)	17.4	17.3	13.7	14.9
Arousal index (events/hour)	110.47	9.7	25.9	16.6
Apnea-Hypopnea Index (AHI; events/hour)	72.36	1.4	6.6	4.3
Respiratory Disturbance Index (RDI; events/hour)	–	–	13.8	13.6
Oxygen saturation (SpO_2) nadir	87%	95%	89%	89%
Time with oxygen saturation (SpO_2) $<$ 90% (in minutes)	–	0.2	0.2	0.1

Abbreviations: BiPAP, bilevel positive airway pressure; MAD, mandibular advancement device.

Discussion

As an autoimmune disease of the neuromuscular junction, MG is characterized by symptoms of weakness and easy fatigability. The condition worsens with excessive effort, but improves with the use of anticholinesterase drugs and rest, and the performance of physical therapy can change the survival of these patients, interfering with quality of life and life expectancy.[1,14]

Other symptoms are also mentioned, and they vary from patient to patient, but may typically include falling of one or both eyelids (ptosis), weakness of the ocular musculature (strabismus), double vision (diplopia), difficulty in swallowing (dysphagia), difficulty in speaking (dysphonia), weakness in the chewing muscles (as a consequence of the mandible drop), or neck tilt, with forward head drop, and limb muscle weakness (with difficulty walking, climbing stairs, raising arms to write, and combing). Weakness of respiratory muscles is a potentially fatal complication.[14]

Patients with myasthenic crisis should be evaluated periodically with measures of maximal inspiratory pressure (PI max), maximal expiratory pressure (PE max), and forced vital capacity. Patients who have vital capacity of 50%, PI max lower than -30 cmH2O, and PE max lower than 40cm H2O, can undergo an attempt at treatment with noninvasive ventilation (BiPAP) and, if it fails, they should be intubated electively to avoid tracheal intubation in the emergency room.

The use of noninvasive ventilation with BiPAP can also be considered in patients with MG with persistent or recurrent weakness after extubation.

An intensive respiratory program including sighs, use of positive end-expiratory pressure (PEEP), frequent aspiration of the bronchial tree, respiratory physiotherapy, change of decubitus, and administration of antibiotic therapy in cases of documented infection should be considered in patients on mechanical ventilation during the myasthenic crisis.

The intraoral MAD is a treatment that maintains anterior traction of the mandible with consequent activation of the chewing muscles and can often be related to TMD.[13] The present report is that of a rare case of MAD treatment in a patient with MG who, although prior to medical treatment reported complaints related to chewing, after medical stability of the disease, MAD treatment was not related to muscle symptoms. Studies[16,17] show that MG causes such repercussions as altered contraction in the masseter muscles, and these symptoms are related to the abnormality in the synaptic junction of these muscle groups.

Patients with MG and other degenerative neuromuscular disorders are usually referred for OSA and/or hypoventilation treatments as the noninvasive positive airway pressure mechanical ventilation that is provided in two cycles with inspiratory pressure support and PEEP phase (BiPAP). The positive bi-level pressure emerged as an alternative to endotracheal intubation and mechanical ventilation in primary lung disorders.[18]

Myasthenia gravis has a specific neuromuscular pathophysiology, and its treatment with MAD, an intraoral appliance, might not be sufficient to resolve mild OSA. In the present report, there was an improvement in the PSG parameters, as well as in the complaint of snoring. Another common complication in individuals with MG is muscular TMD, which, in addition to being common in myasthenia, may also occur as a consequence of the MAD treatment, which in fact did not occur in the patient herein reported.

Although we know that the treatment of choice for OSA in patients with MG is BiPAP, the adherence to MAD therapy is justified by the reported quality of life and sleep of the patient.[19]

In conclusion, although apparently not recommended, MAD might be considered an alternative treatment for OSA in selected and stable patients with neuromuscular disorders without sleep hypoventilation who do not adhere to positive airway pressure. Follow-up with PSG or ambulatorial monitoring is advised, due to the progressive characteristic of the neuromuscular condition.

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Conflict of Interests
The authors have no conflict of interests to declare.

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