CPAP Therapy Reverses Weakness of Myasthenia Gravis: Role of Obstructive Sleep Apnea in Paradoxical Weakness of Myasthenia Gravis

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CASE REPORTS

Fatigability after exercise and restoration of strength by rest are clinical hallmarks of myasthenia gravis (MG). These unique features are originated from a reduced safety factor, which is related to a defect of acetylcholine receptor, and post-exercise exhaustion of neuromuscular junction transmission. Therefore, most patients with MG feel recharged muscle strength and show normal muscle power after nocturnal sleep. As such, worsening of MG symptoms during nighttime is usual. However, in very rare cases, some patients with MG complain fatigability and weakness in the morning, so called "paradoxical weakness (PW)." We report two MG patients with typical PW, diagnosed with OSA by

polysomnography. CPAP therapy successfully improved their morning symptoms and quality of life. So far, the detailed mechanism of PW in MG is unknown; however, our report highlights the possible role of sleep disorders in developing a PW in MG and the therapeutic target for life quality of MG.

Keywords: Myasthenia gravis, paradoxical weakness, obstructive sleep apnea, CPAP

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Myasthenia gravis (MG) is a rare autoimmune neuromuscular disorder characterized by immunological attack on acetylcholine receptor and subsequent defect of neuromuscular junction transmission (NMJT) within motor end plate.¹ Clinically, fatigability after exercise and restoration of strength by rest are clinical hallmarks and associated with an aforementioned "safety factor" of NMJT.^{1,2} However, in rare cases, patients with MG may show a worsening of symptoms on awakening, so-called paradoxical weakness (PW).³ We recently saw two MG patients with PW who were diagnosed with OSA by polysomnography (PSG). We managed them with CPAP therapy, which successfully reversed the PW of MG.

REPORT OF CASES

Case 1

A 60-year-old obese woman visited our clinic because of serious deterioration of muscle strength in the morning. She had weakness in swallowing, eye-opening, and facial expression. Limb weakness was not apparent. Her symptoms usually improved slowly over a few hours of rest. She had been diagnosed with generalized MG and had a thymectomy 5 years previously. She had minimal myasthenic features, such as ptosis and transient dysphagia with low dose pyridostigmine, azathioprine, and prednisolone. Recently, she had weight gain of about 5 kilograms over 2 months. Her body mass index was 28.04 kg/m². On physical examination, she showed a moon face, short neck, central obesity, and buffalo hump-like neck. As she

complained of PW on awakening from sleep in the morning, we evaluated her sleep history. She had loud snoring, and her family members reported frequent apnea during sleep. Furthermore, her symptoms became worse despite a daytime nap. PSG revealed severe OSA, with a respiratory disturbance index of 48.2/h. Desaturation nadir was 71%. Her arousal index was 45.1/h. CPAP titration was done successfully (**Figure 1**). One week of CPAP (pressure at 10 cm H₂O) markedly improved morning weakness. Within a month, PW disappeared without medication adjustment.

Case 2

A 20-year-old female patient was admitted to the hospital because of breathlessness during sleep and extreme fatigue in the morning. Diplopia and ptosis were evident early in the morning. She had been diagnosed with generalized MG 2 years previously and had been complaining of mild bilateral ptosis and diplopia. Despite of several episodes of symptom fluctuation, her MG was stably controlled with nisolone 30 mg, Mestinon 450 mg, and mycophenolate 1 g/day. Until now, she had never experienced a significant exacerbation of MG symptoms on awakening in the morning. She was obese, with body mass index of 32.79 kg/m² and had gained 3-4 kg within the past month. Cushing features were also noticed. She reported loud snoring and apnea, which had worsened recently. PSG revealed a respiratory disturbance index of 23.7/h with mild hypoxemia (desaturation to nadir of 88%). Arousal index was 22.0/h. CPAP (pressure at 8 cm H₂O) therapy promptly improved her morning symptoms.

Figure 1—Hypnogram of diagnostic polysomnography (A) and CPAP titration (B) of case 1.

Note the frequent respiratory disturbances with prominent oxygen desaturation. The breathing abnormalities were significantly worse in REM sleep. Optimal CPAP resolved sleep disordered breathing and reduced arousals.

DISCUSSION

The prevalence of minimally symptomatic or asymptomatic OSA and OSA syndrome in the general population is about 20% and 5%, respectively.⁴ However, the prevalence of OSA in patients with neuromuscular diseases is largely unknown, even in relatively common neuromuscular diseases such as MG. One cross-sectional study to assess the prevalence of OSA in MG showed 36% for OSA and 11% for OSA syndrome.⁵ A recent case report that demonstrated the use of CPAP therapy led to improvement in symptoms of not only OSA but also ocular MG raises the potential association with MG and OSA.⁶

PW is a rarely described clinical feature of MG. We could find only one report for this concept.³ The mechanism of PW has not been elucidated yet.

We hypothesize that PW is either a rare clinical fluctuation of generalized MG or a specific phenomenon confined only to MG with OSA. At all events, muscles are weakened with repeated use, and strength improves by taking a rest. Therefore, we speculate that PW arises from muscular loading and non-restorative sleep in MG with or without OSA. For example, PW can originate from either metabolic or mechanical aspects of nocturnal burdens. It seems that chronic exposure of repetitive hypoxia, despite ongoing respiratory muscular effort,

results in a decreased safety margin (immunological safety factor) of NMJT and subsequent muscular fatigability in morning time. Moreover, sleep disturbance factors such as partial arousal, sleep fragmentation, and sleep deprivation can also contribute to PW, due to disturbed restorative sleep. Additionally, given that MG is an autoimmune disease, the role of OSA in modulating the immune system should be considered as well. Although the direct relationship between OSA and MG in immune-modulation is unknown, sleep apnea may increase the risk of autoimmune disease by T-cell mediated manner.⁷ Sleep deprivation is also associated with reductions in immune response.⁸ Finally, weight gain with or without chronic steroid therapy may have contributed. It can aggravate the severity of underlying OSA or even independently lead to the development of OSA.⁹

In our cases, two patients were obese and had generalized MG. In addition, they had Cushing features and history of recent weight gain as well as chronic steroid medication. No overt aggravating factors of MG were present, except for disturbed sleep. PW is a rare and unfamiliar phenomenon in MG. Without consideration of PW and its possible relationship to OSA, it is highly likely that clinicians might increase a corticosteroid dose to patients.⁵ Hence, early consideration of OSA or related sleep disorders can introduce an adequate management, such as CPAP therapy, and prevent unnecessarily high dosage of corticosteroid to patients showing PW of MG.

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