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Research Report

Excessive Daytime Sleepiness in Patients with Myasthenia Gravis

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Abstract. Excessive daytime sleepiness (EDS) has not been investigated using objective tests in myasthenia gravis (MG). We investigated whether objective measurements of somnolence better detected abnormalities compared with sleepiness questionnaires in MG, and determine if MG patients have EDS. Eight patients with mild-to-moderate MG were recruited. Patients completed maintenance of wakefulness, overnight polysomnography, multiple sleep latency tests, Epworth Sleepiness Scale, and fatigue questionnaires. Seven patients demonstrated EDS on objective testing, while Epworth scores were abnormal in two, and the measures showed poor correlation. Our findings highlight that the ESS may be inadequate to diagnose EDS and lead to under-reporting of daytime somnolence in patients with MG.

Keywords: Myasthenia gravis, sleep, excessive daytime sleepiness, sleep apnea

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction characterized by fatigable weakness. Patients with MG often complain of non-restful sleep and daytime somnolence. Studies of sleep in MG have focused on respiratory function and obstructive sleep apnea (OSA), usually finding a higher rate of OSA compared to the general population [1–3].

Excessive daytime sleepiness (EDS) is an important symptom of OSA. Studies on EDS in MG are conflicting, with some showing a relationship between OSA severity and EDS, and others finding no relationship [1, 3–5]. This may be partially methodological, relying on subjective questionnaires such as the Epworth Sleepiness Scale (ESS) to diagnose EDS. Subjective reporting of sleep state is prone to bias depending on motivation.

There are no studies quantifying increased sleep tendency in MG using objective measures in a sleep laboratory. The aim of this study was to investigate whether objective measurements of increased sleep tendency correlate with subjective sleepiness questionnaires, and reliably detect somnolence in MG.

MATERIALS AND METHODS

Patients

Consecutive patients from a large MG clinic were recruited, with diagnosis based on fatigable weakness, and either abnormal electrophysiology (repetitive nerve stimulation or single-fiber electromyography) or serology (anti-acetylcholine receptor or muscle specific kinase antibodies). Patients had to be over the age of 18, with mild-to-moderate disease severity based on the Quantitative Myasthenia Gravis Score (QMGS <20). QMGS is a categorical scale of severity, from 0 (no signs of MG) to 39 (severe) [6]. Patients needed a stable recent clinical history (no

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crises within 6 months), and stable oral medication doses. Patients with known sleep disorders or respiratory diagnoses were excluded by history. All patients gave informed consent, and the institution research ethics board approved the study.

Sleepiness measures

Objective measures of increased sleep tendency were assessed using the maintenance of wakefulness test (MWT) and the multiple sleep latency test (MSLT), done on successive days (as described in [7]). During the MWT the patient was asked to remain awake in a comfortable chair for 40 minutes, repeated 4 times (0900, 1100, 1300 and 1500 hrs). Patients then underwent overnight polysomnography. The following day, the MSLT was performed, consisting of 4 naps (0900, 1100, 1300 and 1500 hrs), lasting a minimum of 20 minutes and a maximum of 34.5 minutes. If sleep occurred within the first 19.5 minutes, the nap ran for 15 more minutes to assess for rapid eye movement sleep. The MWT and MSLT sleep latencies determined increased sleep tendency.

Subjective sleepiness was assessed using the ESS [8]. Patients rated subjective fatigue on a visual analog scale (VAS) from 0 (no fatigue) to 10 (severe fatigue). To assess impact of fatigue, the modified fatigue impact scale (MFIS) [9] was utilized. Quality of life (QOL) was measured using the validated myasthenia gravis QOL (MG-QOL15) [10]. ESS, VAS, and MFIS results were correlated (Spearman correlation) with the MWT and MSLT sleep-onset latencies. ESS and VAS results were correlated with the MG-QOL15. All patients completed questionnaires to determine sleep hours and habits.

RESULTS

Eight patients were recruited. There were seven females, the mean age was 55 years, and mean BMI was 27.1. Two patients were overweight (BMI 25.9, 28.1) and three were obese (BMI 30.2, 33.8, 33.9). Mean disease duration was 7.6 ($\pm$5.2) years and mean QMGS at screening was 9.6 ($\pm$3.8). One patient was on prednisone and another was taking pyridostigmine (60 mg BID). No patients reported symptoms of insomnia.

Table 1 shows the MWT, MSLT and PSG results. The mean MWT sleep latency was 27.4 ($\pm$10.2) minutes, and the mean MSLT sleep latency was 11.7 ($\pm$5.0) minutes. Seven patients demonstrated increased sleep tendency, being unable to remain awake for the full 40-minute MWT. Four patients had MSLT latencies below 10 minutes. There were no significant periodic limb movement abnormalities, and none had REM sleep behavior disorder. The mean apnea-hypopnea index (AHI) was 12.6, and four had an AHI >5 (suggesting mild OSA or worse). Mean sleep time with oxygen saturation below 90% was 8%, and mean sleep duration was 6.93 hours. Comparing the MWT and MSLT latencies between normal (18.5 to 25) and elevated BMI (>25) patients showed a lower MWT latency in the elevated BMI group (19.7 vs. 35.0 minutes; Student's t-test, $p < 0.05$). There was no difference in MSLT sleep latency or AHI between these groups.

Subjective measures are shown in Table 2. The mean ESS score was 8.6, with 2 patients scoring greater than 10. The mean fatigue VAS score was 47.5 (range 20 to 70). Correlations between objective sleepiness (MWT and MSLT sleep-onset latencies) and subjective measures (ESS, fatigue VAS, MFIS, MG-QOL) are in Table 3. Correlations were weak to moderate, and none were statistically significant. MG-QOL15 correlated strongly with the MFIS ($r = 0.790$, $p = 0.0195$) but not ESS ($r = 0.479$, $p = 0.23$) or fatigue VAS ($r = 0.395$, $p = 0.332$). There were no significant correlations between weakness (measured by QMGS) and objective or subjective sleepiness measures (Table 3).

DISCUSSION

This is the first study to use objective sleep laboratory measures to assess increased sleep tendency in MG patients. We found that objective and subjective measures of somnolence correlated poorly. Two patients (25%) scored over 10 on the ESS, the usual threshold value for clinically-recognized EDS based on interview [11]. This result is similar to other studies [1–3], and using an ESS of >10 the prevalence of EDS was reported as between 15–25%. Prudlo et al. found a mean ESS of 6.7, concluding that subjective EDS is not a feature of MG [3]. A recent study specifically examined EDS and sleep quality in MG, finding that 15% of well-controlled MG patients had an ESS >10 [5]. Objective tests of sleepiness were not performed in these studies. Given the discrepancy between the ESS and MWT findings in our study, it is important to consider that the ESS may not be sensitive enough to detect true sleepiness in patients with MG, and relying solely on the ESS may underestimate EDS [12, 13].

Increased sleep tendency was common in our cohort, whether measured by MWT or MSLT, and compared to published norms [14, 15]. Seven patients demonstrated increased sleep tendency on the MWT, being unable to

Table 1
Demographics and sleep study results

Subject	Age (years)	BMI	MSLT latency (min)	MWT latency (min)	Apneal/ Hypopnea Index	O2 Nadir (%) Nadir (%)	Sleep duration (hours)	Sleep Efficiency (%)
1	74	22	20	29.6	12.3	83	6.42	85.7
2	67	30.2	13	28.875	34.8	80	6.49	79.7
3	62	33.9	10	36	30.3	69	5.04	62.1
4	28	22.9	20	16.5	0.3	91	6.52	78.4
5	36	33.8	20	35.3	1.8	91	8.11	85.7
6	82	25.9	2.5	10.4	21.2	83	6.50	74.6
7	38	28.1	8.5	40	0.1	92	9.08	89.9
8	55	20.2	7	22.4	0.1	93	7.29	89.6
Mean	55.3	27.1	12.6	27.4	12.6	85.2	6.93	80.7

BMI = Body mass index; MSLT = Mean Sleep Latency Test; MWT = Maintenance of Wakefulness Test.

Table 2
Subjective measures of sleepiness, fatigue and quality of life

Subject	ESS	VAS	MFIS	MG-QOL15
1	16	40	48	13
2	3	40	29	8
3	3	70	53	28
4	19	50	63	29
5	9	60	43	29
6	3	50	39	10
7	6	50	17	7
8	10	20	54	15
Mean	8.6	47.5	43.3	17.4

ESS = Epworth sleepiness scale; VAS = Visual analog scale (fatigue); MFIS = Modified Fatigue Impact Scale; MG-QOL15 = Myasthenia gravis Quality of Life-15.

remain awake for the entire 40-minute period and suggesting decreased alertness and increased tendency to fall asleep. At least 75% of normal people should be able to stay awake on all four MWT tests [14]. On the MSLT, which has less surface validity for detecting functional alertness impairment, four patients (50%) fell asleep before 10 minutes. The 2014 International Classification of Sleep Disorders 3 considers an MSLT latency >10 minutes as normal, whereas age-based estimates suggest that >11.2 minutes is more accurate for patients aged 50 to 60 [15, 16]. It is important to note that in the context of our study, results from the MWT and MSLT are used as measurements of increased sleep tendency rather than conclusive diagnostic or gold-standard tests for EDS.

Half of our patients were found to have OSA. Nicolle et al. found that more MG patients with OSA had an ESS score >10, compared to MG patients without OSA (non-statistically significant) [2]. In the seven patients with increased somnolence in our cohort, 4 had OSA as a likely etiology. Of the 3 remaining patients, one had elevated BMI (33.8) without upper airway resistance, which has been independently associated with EDS [17, 18]. These findings highlight that multiple factors contribute to somnolence in patients with MG.

One previous report found a significant correlation between sleep quality and QOL in MG patients [5]. In our study, MG-QOL showed a strong positive correlation with patient-reported fatigue but not sleepiness. This suggests that the concept of "fatigue" and "sleepiness" are different. Fatigue likely captures a subjective lack of energy for physical and cognitive tasks in addition to sleepiness, and this has a strong impact on determining QOL for MG patients [19]. To disentangle the components of sleepiness that contribute to perceived fatigue, future studies could explore the impact of treatment of sleep disorders in these patients.

A major strength of our study was the systematic collection of objective detailed MWT, PSG and MSLT data. As our study is a hypothesis-generating pilot study,

Table 3
Correlations between objective and subjective sleepiness, and quality of life

		ESS	VAS	MFIS	MG-QOL15	QMGS at Screening
MWT Sleep	Spearman r	−0.1708	0.4051	−0.3571	−0.1437	−0.2684
Latency	*p*-value	0.686	0.3194	0.3851	0.7342	0.5204
MSLT Sleep	Spearman r	0.5500	0.1509	0.2684	0.5154	0.0000
Latency	*p*-value	0.1578	0.7212	0.5204	0.1911	1.0000
MG-QOL 15	Spearman r	0.4786	0.3952	**0.7904**	–	0.1718
	p-value	0.2302	0.3325	**0.0195**		0.6841
QMGS at Screening	Spearman r	−0.4000	0.1258	−0.1952	–	–
	p-value	0.3263	0.7666	0.6432		

MSLT = Mean Sleep Latency Test; MWT = Maintenance of Wakefulness Test; ESS = Epworth sleepiness scale; VAS = Visual analog scale (fatigue); MFIS = Modified Fatigue Impact Scale; MG-QOL15 = Myasthenia gravis Quality of Life –15; Bold = Statistically significant.

our primary limitation is the small sample size and the lack of comparison with an appropriately powered control group. Sleepiness and fatigue confounders were limited by recruiting patients without known primary sleep pathology. We recruited MG patients with mild disease and thereby may underestimate EDS. In addition, the large imbalance in gender (7 of 8 patients were female) impairs generalizability of the results though we would expect that this might actually bias against our findings as women have less obstructive sleep apnea, which is known to contribute to sleepiness. We cannot exclude a first night effect influencing sleep quality and the MSLT results in 4 patients with mildly reduced sleep efficiency, though this is the routine assessment of sleep disorders in a clinical context. Furthermore, a first night effect could not explain the abnormal MWT findings, as this test would be biased in the opposite direction, and the MWT likely better captures alertness following a night of sleep "in the real world". We do not have sleep diary, actigraphy data or PSG data in the weeks leading up to the MSLT and MWT to confirm sleep quantity and quality; however, a sleep questionnaire completed prior to testing confirms typical sleep patterns including usual bed and wake times.

Our findings highlight that the ESS may be inadequate to detect increased somnolence in patients with MG and may lead to inaccurate estimations of its prevalence, especially in patients with mild MG. As this study was an exploratory pilot study, larger studies adequately powered to detect differences between control and MG are needed to confirm these findings. Clarifying the relationship between OSA and EDS is especially important for MG patients, since treatment of OSA and EDS may improve neuromuscular weakness [20].

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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