Sleep and breathing Study in Myasthenia Gravis

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Abstract

objectives: Myasthenia gravis (MG) is an autoimmune disease disturbing sleep architecture. We carried out the study to find if there is any sleep disturbance and if there is any relationship between both. Methods: We performed clinical evaluation, Polysomnography (PSG), for 20 patients presenting with MG and 20 healthy subjects as a control group. Results: Decreased total sleep time (p = 0.011), decreased sleep time of stage I and II (p = 0.021. 0.029 respectively), decreased REM latency (p = 0.001), decreased percentage of stage III and IV (p = 0.004), increased number of awakening (p = 0.001), decreased efficiency of sleep (p = 0.006) and significant sleep disordered breathing (SDB) {central apnea with P value (0.007)}. Conclusion: In contrast with the control group, MG patients had marked sleep disruption, as regards sleep stages parameters and efficiency with occurrence of SDB.

Key Words: Myasthenia Gravis; Polysomnography; Sleep; Sleep Disordered Breathing.

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Introduction:

Myasthenia gravis is an autoimmune disease caused by antibodies destroying postsynaptic nicotinic acetylcholine receptors (AChR); or protein included in neuromuscular transmission likes a muscle-specific receptor tyrosine kinase or lipoprotein-related protein 4. (1, 2, 3)

Myasthenia gravis can affect any of the voluntary skeletal muscles (e.g. eyes, face, neck, legs, and trunk) leading to easy fatigability and muscle weakness. Approximately 70% of patients showed nearby all symptoms of MG, whilst the other 30–40% of the patients manifested with fatigue in respiratory, oropharyngeal muscles contributing to sleep-disordered breathing. (4)

Apnea was defined as an oronasal airflow cessation for ≥ 10sec, while, hypopnea was defined as > 50% reduction in airflow for 10 sec followed by either ≥3% oxygen desaturation or an arousal. (5, 6)

Sleep-disordered breathing leads to increased number of nocturnal awakenings, reduced sleep efficiency, and excessive daytime sleepiness. (7, 8)

Aim of the Work:

The purpose of this study aimed to study sleep architecture and find if there is any sleep disordered breathing in patient with MG and if there is any relationship between both.

Subjects and Methods:

This study is a cross-sectional case control study with twenty patients (15 females and 5 males) with a mean age 30.65 ± 13.99 presenting with myasthenia gravis (MG) diagnosed (clinically and electrophysiological).

The age and sex of twenty matched healthy controls (15 females and 5 males), with a mean age 28.90 y ± 8.86.

All included patients and controls subjected to the following the polysomnographic parameters.

Excluded from the study patients with any associated medical or metabolic disorder such as hepatic or renal dysfunction, thyroid or parathyroid disease.

All participants were clarified by the research and written informed consent was collected from them prior to starting the research.

All included patients subjected to the following:

1)History taking with especial stress on age of onset, course, duration, degree, distribution of weakness (ocular, bulbar, limb weakness) and diurnal variation of symptoms. Symptoms of respiratory and other system affection.

2)**Sleep history**: STOP questionnaire: The STOP questionnaire includes 4 questions related to snoring, tiredness during daytime, observed apneas, and the presence of high blood pressure. A score ≥ 2 places an individual into a high-risk category for OSA. (9)

3)**Neurological examination: Full general and neurological examination:** Presence of ptosis, bulbar manifestation, respiratory affection, distribution of weakness and degree of affection. Patients were clinically graded for severity of illness according to The Myasthenia Gravis Foundation of America (MGFA). (10,11)

4)**Laboratory investigations:** Routine laboratory tests and Arterial blood gases & pulmonary function tests to evaluate respiratory functions and help in clinical classification of MG patients according to The Myasthenia Gravis Foundation of America (MGFA).

5)**Imaging studies:** Chest x ray and Chest computerized tomography (CT).

6)**Electrophysiological assessment:** were carried out using a Nihon Kohden® apparatus to diagnose MG patients thorough repetitive Nerve Stimulation (RNS) and single fiber electromyography (SFEMG). (12, 13, 14, 15)

7)**Polysomnographic study:** During the night, polysomnography was carried out for both patients and controls, thorough a SOMNOscreenTM plus PSG+, medical diagnostic polysomnogram, Germany. In accordance with recommendation of American Academy of Sleep Medicine (AASM), the following was recorded; Electroencephalography (EEG), Electrooculogram (EOG), ECG, continuous Electromyography (EMG) of the tibialis anterior and submentalis muscles, airflow monitoring with cannula inserted in the nostrils and over the mouth, ventilatory effort by strain gauges, saturation of arterial oxygen (O2) with pulse oximetry, upper airway sound, and body position. The recording time ranging from 6 to 8 hours. (16)

Methodology of Statistics:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables. (17). For comparing categorical data, Chi square (χ2) test was performed. Exact test was used instead when the expected frequency is less than 5. (18) P-values less than 0.05 were considered as statistically significant.

Results:

A- **Descriptive results**:

1- **Age:**

The mean age of patients was 30.65 ± 13.99 y and control was 28.90±8.86 y.

Table (1): Comparison between patients and control as regard age

	Patients					Control					P
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	value
Age	30.65	13.99	32.00	10.00	50.00	28.90	8.86	32.00	15.00	40.00whi	0.602

2- Sex:

Table (2): Comparison between patients and control as regard sex

		Patients		Control		P
		Count	%	Count	%	value
Sex	Female	15	75.0%	15	75.0%	1
	Male	5	25.0%	5	25.0%	

3- Body mass index: -

The mean body mass index of patients was 24.86 ±3.71 kg/m2 and control was 26.95±3.08kg/m2.

Table (3): Comparison between patients and control as regard body mass index

	Patients					Control					P
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	value
BMI	24.86	3.71	24.30	19.90	30.20	26.95	3.08	27.80	20.90	30.80	0.060

A- Clinical Results:

1-Duration of the illness:

The mean duration of illness 3.28 ± 2.24 y.

Table (4): Duration of illness

	Patients				
	Mean	SD	Median	Minimum	Maximum
Duration	3.25	2.24	2.50	1.00	7.00

2- **Severity of the illness**:

For grading of illness in myasthenic patients regarding The Myasthenia Gravis Foundation of America (MGFA), patients were divided into 5 subgroups (see table 5, figure 1). The number and percentages of patients in each subgroup were:

Class I: two patients representing 10% of patients;

Class IIA: four patients representing 20% of patients;

Class IIB: six patients representing 30% of patients;

Class IIIB: six patients representing 30% of patients;

Class IVB: two patients representing 10% of patients.

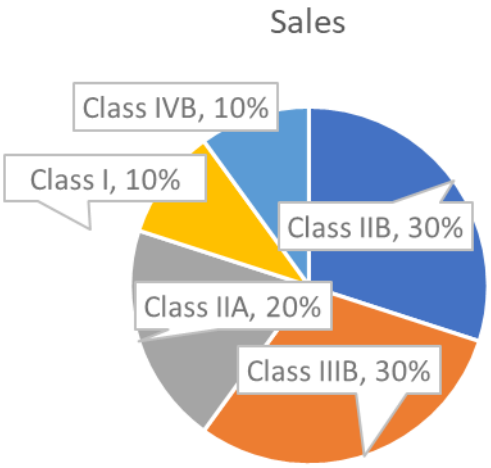


Figure (1): Number and percentages of MG patients in this study regarding The Myasthenia Gravis Foundation of America (MGFA).

Table (5): Severity of the illness

		Patients	
		Count	%
Severity	I	2	10.0%
	IIA	4	20.0%
	IIB	6	30.0%
	IIIB	6	30.0%
	IVB	2	10.0%

3-**Sleep apnea questionnaire**:

All Patients were subjected to sleep apnea questionnaire. If patient answered "yes" to any questions he or she was considered to have sleep apnea. In the study, ten patients (50%) answered "Yes" while the other ten patients (50%) answered "No".

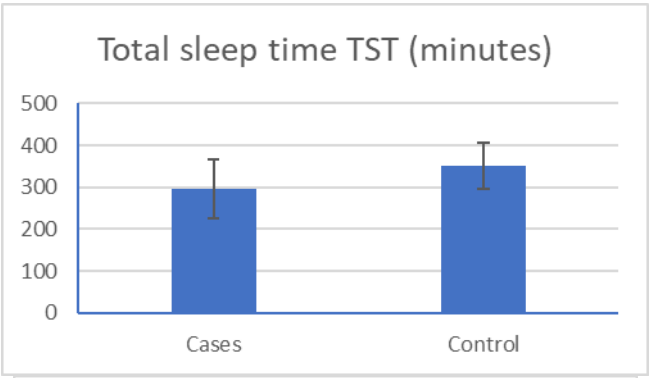
C- **Polysomnography Results**:

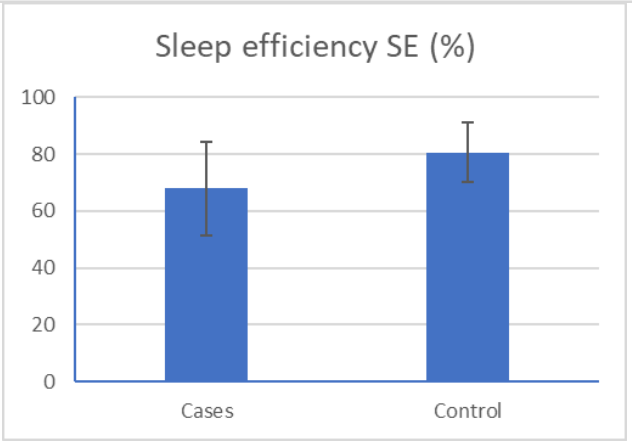
The means and standard deviations of sleep architectures for patients with MG and control group are demonstrated in Table 6.

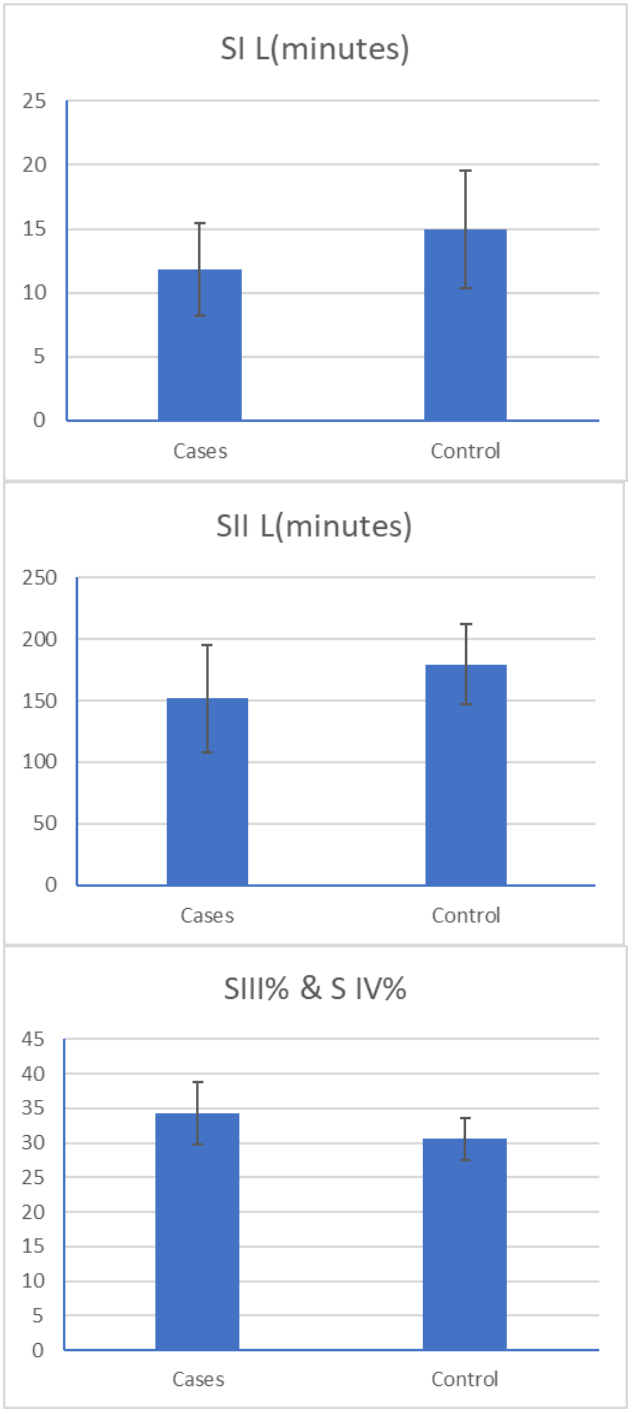
Table (6): Comparison of sleep architectures (recorded by polysomnography) between MG patients and controls.

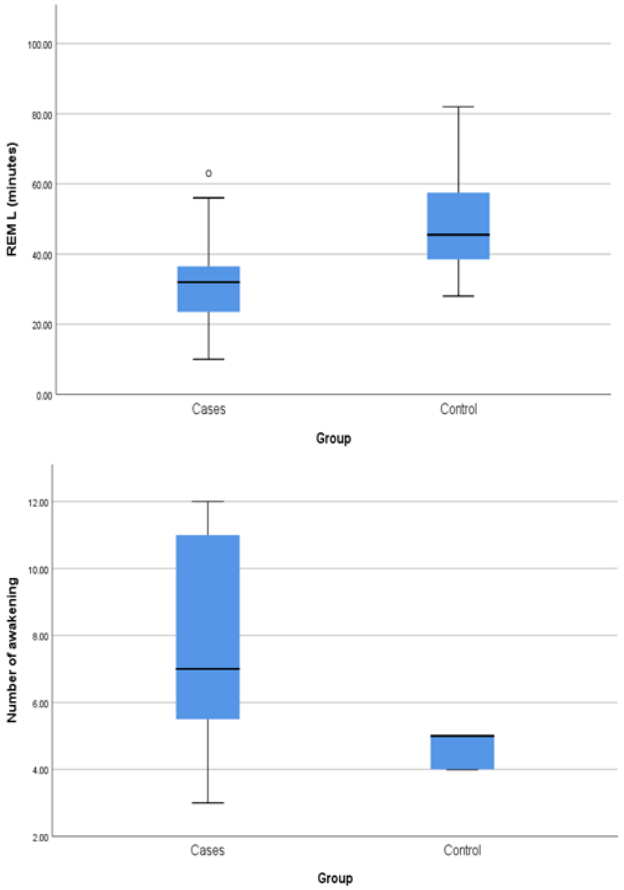
	Patients					Control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Total sleep time TST (minutes)	296.80	69.96	304.00	178.00	414.00	350.00	55.21	358.00	249.00	437.00	0.011
Sleep onset (minutes)	44.60	39.70	39.50	0.00	110.00	23.10	20.29	13.50	1.00	57.00	0.265
Sleep efficiency SE (%)	67.98	16.43	67.65	44.60	95.30	80.62	10.38	81.65	64.50	96.30	0.006
Number of awakening	7.85	2.76	7.00	3.00	12.00	4.60	0.50	5.00	4.00	5.00	< 0.001
SI L(minutes)	11.80	3.64	11.50	5.00	19.00	14.95	4.58	15.50	9.00	23.00	0.021
SII L(minutes)	151.75	43.70	151.00	82.00	243.00	179.55	32.80	184.50	116.00	238.00	0.029
SIII &S IV L (minutes)	101.55	27.44	95.00	57.00	167.00	106.55	17.17	109.50	73.00	137.00	0.494
REM L (minutes)	31.70	12.35	32.00	10.00	63.00	48.95	14.31	45.50	28.00	82.00	< 0.001
SI%	4.06	1.07	4.10	2.00	5.60	4.27	1.18	4.40	2.30	5.90	0.568
SII%	50.74	5.07	49.80	43.00	61.80	51.22	3.18	51.60	45.90	56.00	0.719
SIII% & S IV%	34.27	4.54	33.90	27.10	44.80	30.56	3.01	30.85	24.00	35.10	0.004
REM%	14.90	3.38	15.20	10.20	19.50	13.95	3.12	14.50	8.80	20.40	0.359

Figure (2): Comparison between patients and control as regard total sleep time, sleep efficiency, SI latency, SII latency, REM stage latency, stage III and stage IV percentage and number of awakenings









The means and standard deviations of respiratory indices for patients with MG and control group are demonstrated in Table 7.

Table (7): Comparison of respiratory indices (recorded by polysomnography) between patients with MG and control group.

	Patients					Control					p value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Central hypopneas	1.90	1.94	1.50	0.00	6.00	0.70	0.86	0.00	0.00	2.00	0.068
Central apnea	0.85	0.81	1.00	0.00	2.00	0.15	0.37	0.00	0.00	1.00	0.007
Obstructive apnea	0.35	0.49	0.00	0.00	1.00	0.30	0.47	0.00	0.00	1.00	0.799
Mixed apnea index	0.03	0.06	0.00	0.00	0.20	0.00	0.00	0.00	0.00	0.00	0.429
SDB in REM	4.35	3.72	4.00	0.00	11.00	2.35	1.63	3.00	0.00	5.00	0.127
SDB in NREM	2.20	1.96	2.00	0.00	6.00	1.20	0.83	1.00	0.00	2.00	0.157

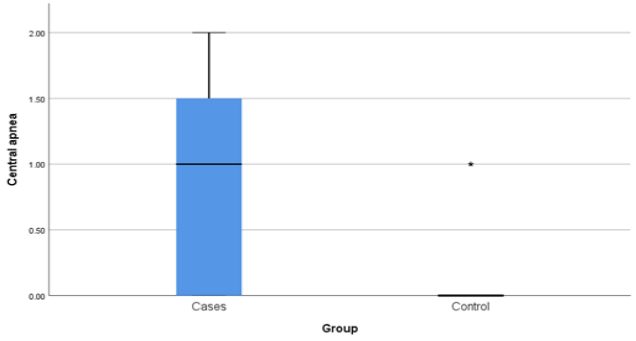


Figure (3): Comparison between patients and control as regard respiratory indices

Discussion

The current study was undertaken to analysis the presence of sleep disordered breathing in patient with MG and to find any relation between both in MG patients.

In this study, polysomnography for MG patients showed sleep disordered breathing. The results of patients differed from that of age and sex matched control group.

In this study, MG patients experienced both apneas and/or hypopneas, mostly occurred in rapid eye movement (AHI in REM) (i.e., patients experienced respiratory disorders mainly in REM sleep). This is mostly due to diaphragmatic weakness, as diaphragm assumes all respiratory function during REM sleep so diaphragmatic weakness causes respiratory disturbance in REM.

Also, Ezequiel Fernandes Oliveira et al. reported that 64% of MG patients scored as sleep apnea, mildly in 28%, moderately in 12%, and severely in 24% of patients. During the overall sleep period, they reported the mean AHI was 16.5 ± 18.9 and 9.50 (2.95-26.95) was the median value. An AHI of 25.3 ± 21.7 was reported during REM sleep and 15.8 ± 18.8 during NREM sleep. (19)

Also, Culebras found that diaphragmatic dysfunction, whether neurogenic as in motor neuron disease, phrenic nerve paralysis, or neuromuscular as in myasthenia gravis and muscular dystrophies, during REM sleep will affect breathing. (20)

While Nicolle et al. found the majorities of obstructive events in MG patients were hypopneic and occurred in NREM sleep. They suggested that oropharyngeal weakness was more important than diaphragmatic weakness. (21)

In this study, these respiratory events were commonly hypopneas of central type, then central apneas and the least was obstructive apneas.

Chokroverty et al. reported that in neuromuscular disorders over 90% of the respiratory events were scored as hypopneas; only 1.5% of all events were apneas of which 60% were of central type. (22)

While, Prudlo et al. studied thorough PSG the prevalence of SDB in 19 patients with MG and 4 patients were found to have an apnea hypopnea index (AHI) of > 10/h without a central event. (23)

In this study, the respiratory events that had been evaluated as obstructive sleep apnea (OSA) can be attributed to the refine patient selection with lower index of body mass (BMI) (mean =24.86 kg/m2) as 85% of patients have BMI <30, and/or OSA may be attributed to young age of patient (mean=30.65y). Both the previous factors (obesity and old age) were included to other studies and were claimed to cause increase percentage of OSA so in this study we tried to overcome these factors that may affect results.

This goes in accordance with Sung Jae Heo et al., they studied 18 MG patients with OSA (n = 7) and without OSA (n = 11) and found the incidence of OSA is high in men and obese MG patients. (24)

In Nicolle et al. study, there were many risk factors for OSA as older age of patients (mean=66.1y) and greater BMI mean = (34.1kg/m2). (21)

Banno & Kryger reported that in obese patients, fat accumulation in and around the abdomen and ribcage reduce thoracic compliance and functional residual capacity, causing further breathing work with subsequent fatigability. (25)

Shochat & Pillar attributed the increased incidence of OSA to an age-related decline in upper airways muscle tone, causing tissue to collapse in the pharynx. (26)

Malhortra et al. explained that the increased sleep apneas incidence in elderly attributed to age related anatomical changes in the pharynx leading to collapsibility of the upper airway. (27)

Conclusion

Myasthenia gravis patients had marked sleep disruption, as regards sleep related breathing, in the form of apneas and hypopneas of central type mainly in REM sleep,

Sleep disordered breathing was significantly increased in REM sleep, this support the theory that there are central abnormalities in patients complain of myasthenia gravis, this have been attributed to dysfunction of central nicotinic receptor.

Recommendations

Patients subjected to the study preferred not to be on corticosteroid medication, Performing multiple sleep latency (MSLT) for diagnosis of excessive daytime sleepiness.

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