Study Protocol
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Cross-sectional analysis and prospective observational study of sleep quality, lung function, ventilatory muscle strength, ventilatory patterns, autonomic nervous activity, disease severity, clinical status and quality of life in Myasthenia Gravis: a research protocol.

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Abstract
Introduction: The presence of sleep disorders in Myasthenia gravis (MG) patients, can negatively affect the ventilation and the mechanics of breathing in patients with neuromuscular diseases. Some studies have shown a poor quality of sleep, excessive daytime sleepiness and the presence of sleep disordered breathing, while others did not observe a positive correlation. The aim of the study is to investigate sleep quality, lung function, ventilatory patterns, autonomic nervous activity, disease severity, clinical status and quality of life in clinically stable MG patients. **Method**: We propose a cross sectional analysis and prospective observational study of sleep quality, lung function, ventilatory patterns, autonomic nervous activity, disease severity, clinical status and quality of life in MG patients which will be conducted at the Sleep Laboratory of Nove de Julho University and the Neuromuscular Research Department of the Federal University of São Paulo. The design, conduct, and reporting of this study will follow the rules of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. The protocol will includes body weight; height; body mass index; circumferences of the neck, waist, and hip; heart and respiratory rates; Mallampati index; maximum ventilatory pressures; spirometry; and standard overnight polysomnography, as well as the administration of specific questionnaires addressing the risk of obstructive sleep apnoea, excessive daytime sleepiness and HRQoL. Moreover, specific questionnaires addressing sleep apnoea; excessive daytime sleepiness; symptoms of stress, depression, anxiety, disease severity, clinical status and quality of life will be administered. The 8 outcome variables which will be measured include subjective sleepiness Epworth Sleepiness Scale (ESS), risk of OSA through The Berlin Questionnaire, stress and its manifestations by The Inventory of Symptoms of Stress for Adults (LIPP), anxiety and depression by The Hospital Anxiety and Depression Scale (HAD), general quality of life questionnaire using The Short Form 36 (SF36) and specific outcome measure MGQOL 15, MG Composite Scale and The Quantitative Myasthenia Gravis Score. **Discussion:** This protocol expects to identify the presence and severity of sleep disorders, changes of autonomic nervous activity, HRQoL and consequently contribute to an earlier diagnosis, thus reducing the impact on quality of life of MG patients.
Keywords: Myasthenia Gravis; Sleep; Pulmonary Function; Autonomic nervous activity; Disease severity; Clinical status.
Trial registration: The protocol for this study is registered with the Brazilian Registry of Clinical Trials (ReBEC RBR-7ckpdd) and World Health Organization under Universal Trial Number UTN: (U1111-1147-7853).

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INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disease characterised by progressive weakness and easy fatigability of skeletal muscles due to an abnormality in the synaptic junction between nerve and muscle fibres. The severity of the disease depends on the number of muscle groups involved and ranges from mild cases with purely ocular symptoms to severe cases with generalized weakness, including respiratory failure and renal failure. Deaths related to cardiovascular disease in MG patients occur at a trend similar to the general population.[1]

Myasthenia gravis is becoming increasingly common, affecting 1 in every 10,000 Americans between the ages of 20 and 40 years, with women being affected more often than men at a ratio of 3:2.[2]

According to the classification of Osserman and Genkins[3], MG was initially divided into I, II-A and II-B, III and IV, in relation to the onset of symptoms, their severity and their distribution in the muscle groups. Approximately 70% of patients are classified IIa and IIb, as generalized MG.

In the initial phase of the disease is observed impairment of respiratory muscles in only 1-4% of patients, however, in the later stages we observed 60-80% involvement. Of patients with the generalized form, 30-40% will develop some type of involvement of the respiratory musculature with the course of the disease.[4]

In 2000,[5] for the purpose of scientific standardization, this classification was changed by the American Foundation for the Myasthenia Gravis follows:

(I) Any ocular muscles weakness; may have weakness of eye closure; strength of all other muscles being normal.

(II) Mild weakness affecting other than ocular muscles, may also have weakness of ocular muscles of any severity. IIa: predominant affecting limb, axial muscles or both. May also have lesser involvement of oropharyngeal muscles; IIb: predominantly affecting oropharyngeal, respiratory muscles or both. May also have lesser or equal involvement of limb, axial muscles or both.

(III) Moderate weakness affecting other than ocular muscles, may also have ocular muscles weakness of any severity. IIIa: predominantly affecting limb, axial muscles or both. May also have lesser involvement of oropharyngeal muscles; IIIb: predominantly affecting oropharyngeal, respiratory muscles or both. May also have lesser or equal involvement of limb, axial muscles or both.

(IV) Severe weakness affecting other than ocular muscles, may also have ocular weakness of any severity. IVa: predominantly affecting limb and/or axial muscles. May also have lesser involvement of oropharyngeal muscles; IVb: predominantly affecting oropharyngeal respiratory muscles or both. May also have lesser or equal involvement of limbs, axial muscles or both.

(V) Defined by intubation with or without mechanical ventilation, except when employed during routine postoperative management. The use of feeding tube without intubation places the patient in class IVb.

The progression of weakness in MG usually occurs in a cranio-caudal direction. Initially, the affected muscles include the muscles controlling eye and eyelid movement; facial muscles; the muscles of mastication, swallowing, and phonation; and the neck, shoulder, and hip muscles.[6]

The respiratory manifestations are generally attributed to the weakness of the diaphragm and other muscles of the chest wall; however, obstruction of the upper airway could also contribute to these symptoms. The weakness of intercostal muscles and diaphragm leads to dyspnoea on exertion or at rest. The orthopnoea with rapid resolution on sitting up and asynchronous movement of diaphragm are important clinical signs of neuromuscular breathlessness.[7-9]

The presence of sleep disorders in patients with neuromuscular diseases is not well documented in the scientific literature and often is attributed to symptoms of this neurological disease such as daytime sleepiness and fatigue. Furthermore, the symptoms often develop insidiously, which makes it difficult for patients to perceive the disease; however, sleep disorders, particularly sleep disordered breathing (SDB), appear as a major cause of morbidity and mortality in patients with neuromuscular diseases. Therefore, it is important that health professionals recognise the manifestations of sleep disorders in this population.[10]

Sleep disorders can negatively affect the ventilation and the mechanics of breathing in patients with neuromuscular diseases, and SDB may be associated with worsening of cardiopulmonary function. Currently, there are few studies which correlate sleep breathing disorders in MG patients, although some suggest that respiratory disorders may occur in these patients.[11,12]

Obstructive sleep apnoea (OSA) is a respiratory disease characterised by the collapse of the upper airway during sleep in predisposed individuals. After chronic obstructive pulmonary disease and asthma, OSA is the most important and widespread respiratory disease affecting 3%–7% of the male population and 2%–5% of the female population between 40 and 65 years of age in the Western world.[13] In Brazil, the prevalence of OSA in general population is even higher, at 24.8% in men and 9.6% in women, according to a recent epidemiological study conducted in the city of São Paulo.[14]

The increased collapsibility of the upper airway is a major determinant of OSA,[15,16] but the mechanism responsible for collapse of the pharynx during sleep remains unclear. Researchers have identified anatomical factors,[17,18] neuromuscular control factors,[19,20] and the

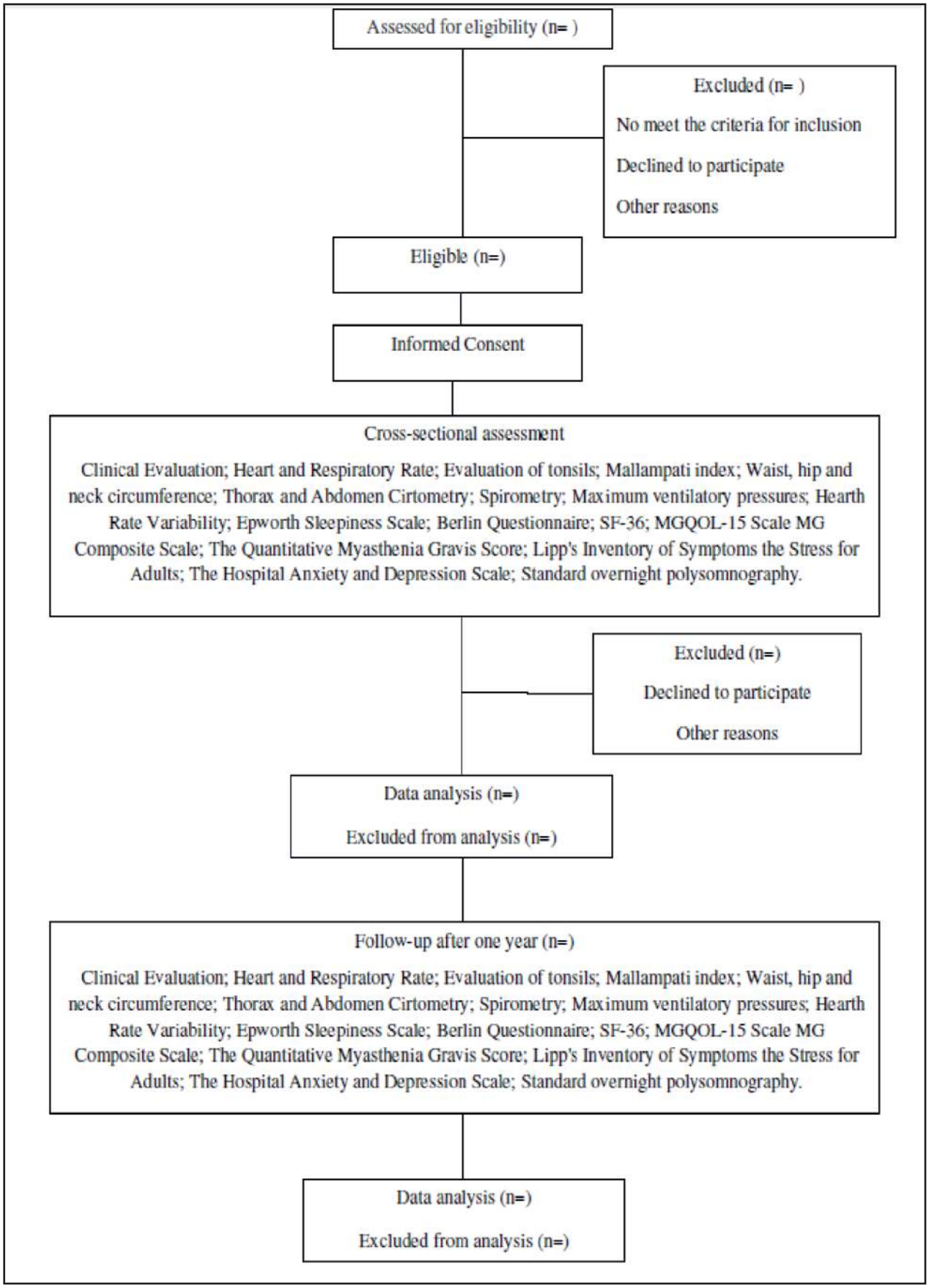

Figure 1. Flowchart of the study.

net deposits of fat[21] which may lead to increased collapsibility of the pharynx during sleep.

In some neuromuscular diseases, is already well described in the literature that sleep may compromise the quality of gas exchange due to change of the respiratory pattern resulting in sleepdisordered breathing. Unfortunately, little is known about the possible relationship between MG, sleep quality and disease severity. Some studies have shown a poor quality of sleep, excessive daytime sleepiness and the presence of sleep-disordered breathing, while others did not observe a positive correlation. However, these studies involved a small sample of patients and not all were made through basal nocturnal polysomnography.

Therefore, given the current state of the art, inconclusive and scarce justifies a study of sleep quality and severity of the disease that can possibly contribute to the scientific literature in order to change the course of the disease, improve quality of life and reduce the considerable costs on patients with MG.

The aim of the current study is to investigate sleep quality, lung function, ventilatory patterns, autonomic nervous activity, disease severity, clinical status and quality of life in clinically stable MG patients.

METHOD

Study design

An cross-sectional analysis and prospective observational study of sleep quality, lung function, ventilatory patterns, autonomic nervous activity, disease severity, clinical status and quality of life in MG patients will be carried out at the Sleep Laboratory of the Post-Graduate Master's and PhD degree in Rehabilitation Sciences at the Nove de Julho University and the Neuromuscular Disease Department of the Federal University of São Paulo. The design, conduction, and reporting of this study will follow the norms of the The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies (Figure 1).

Ethical considerations

The study will be conducted in accordance with the ethical standards established in the 1961 Declaration of Helsinki (as revised in Hong Kong in 1989 and Edinburgh, Scotland, in 2000) and is in compliance with the Regulatory Guidelines and Norms for Research Involving Human Subjects of the National Health Board of the Brazilian Health Ministry issued in October 1996. This protocol received approval from the Human Research Ethics Committee of Nove de Julho University (Brazil) under process no. 360.488 and is registered with the World Health Organization (WHO) under Universal Trial Number (UTN) U1111-1147-7853 and the Brazilian Registry of Clinical Trials (REBEC) RBR -7ckpdd. A signature of informed consent will be required, and subjects will be allowed to withdraw from the study at any time with no negative consequences.

All procedures of this study protocol will be of a personal, confidential nature, subject to therapist/patient confidentiality. Patients diagnosed with sleep disorders will be referred immediately for adequate treatment in order to correct your disease.

Subjects

Subjects with MG will be recruited prospectively from the Neuromuscular Diseases Department from the Federal University of Sao Paulo and sent to the Sleep Laboratory of the Nove de Julho University, Sao Paulo (Brazil). Participants will be recruited consecutively and screened for eligibility using a standardised protocol. The eligibility criteria are described below.

Inclusion criteria comprise 18–65-year-old patients of both sexes diagnosed with clinically stable MG, who agree to participate in this study by signing the Instrument of Consent. The study will exclude subjects with any of the following: ischemic and dilated heart disease; episodes of acute decompensation in the two months prior to the study protocol; primary heart valve disease; acute or chronic cardiopulmonary or neuromuscular diseases; history of recent surgical procedures in the thoracic region; history of stroke; mental instability; drug use; and alcohol abuse.

Sample size calculation and statistical analysis

A previous study by Amino et al.[22] observed an apnea–hypopnea index (AHI) of (mean ± standard deviation) 11.9 ± 6.3 apnoeas or hypopnoeas per hour among MG patients with SDB (AHI ≥ 10) and without SDB (AHI = 4.4) who underwent a polysomnography.

The sample size of our protocol was set at 20 patients in order to detect myasthenia gravis patients with SDB, which will result in a statistical power of 90%, using a two-sided α of 5%. The total sample size will include 23 patients to account for a 15% loss. The Kolmogorov-Smirnov test will be used to verify the normality of distribution of continuous variables. A descriptive analysis will be performed, with the data expressed as either mean and standard deviation or median values and 95% confidence intervals, as appropriate. Comparisons between groups will be performed using Student's t-test or Mann–Whitney U test according to the type of distribution. In addition, a logistic regression analysis of continuous factors with categorical responses will be performed. The statistical analysis will be performed by an experienced statistician using the SPSS® version 16.0 programs (SPSS Inc., Chicago, IL, USA). A 5% level of significance and 95% confidence interval will be applied.

EVALUATION PROTOCOL

Clinical Evaluation

The initial population of MG patients will be asked to be part of the study, and all procedures will be clarified. Those subjects who agree to participate will undergo a detailed patient history; physical examination involving determination of blood pressure, heart and respiratory rates, anthropometric data, circumference measurements (hips, waist and neck); evaluation of tonsils; and Mallampati index. Following the medical examination, the participants will perform spirometry, manovacuometry, a standard overnight polysomnography, and heart rate variability analysis (HRV).

Moreover, specific questionnaires addressing sleep apnoea; excessive daytime sleepiness; symptoms of stress, depression, anxiety, disease severity, clinical status and quality of life will be administered. The 8 outcome variables which will be measured include subjective sleepiness Epworth Sleepiness Scale – ESS[23], risk of OSA through Berlin questionnaire[24], stress and its manifestations by The Inventory of Symptoms of Stress for Adults – LIPP[25,26], anxiety and depression by The Hospital Anxiety and Depression Scale – HAD[27-30], general quality of life questionnaire using The Short Form 36, SF-36[31,32] and specific outcome measure for MG - MG--QOL 15[33,34], MG composite scale[35-37] and The Quantitative Myasthenia Gravis Score[38-40]. All subjects will be submitted to the evaluation protocol described below.

Data acquisition and interpretation of the index tests and reference standards will be completed by investigators who are blinded (masked) to the results and other clinical information.

Physical Examination

Weight and height evaluation will be performed through an electronic balance (model 200/5, Welmy Industria e Comercio Ltda, Sao Paulo, Brazil), and BMI will be calculated using the classification of the WHO.[41] For the assessments of tonsils and Mallampati index, subjects will be in the sitting position and instructed to open the mouth as wide as possible.[42, 43] The measurements of neck circumference will be performed with a metric acrylic tape (width, 7 mm). The site of the measurements will be standardised. Neck circumference will be measured with the subject in the sitting position at the edge of the cricoid cartilage.[44]

LUNG FUNCTION TESTS

Spirometry

Spirometry was performed according to the recommendations by the ATS/ERS task force for standardization of lung function testing,[45] and national guidelines for the execution of lung function tests, calibration and equipment maintenance by the Brazilian Society of Pneumology.[46]

The pulmonary function test was done during the day, seated in a comfortable position, with the body erect and the upper limbs unsupported, on a flow spirometer KoKo® PFT Spirometer System Version 4.11 (nSpire™ Health, Inc., Louisville, CO, USA). Post-bronchodilator spirometry was performed after two puffs of salbutamol (400 µg) administered with a Spacer (Volumantic; GlaxoSmithKline®) in all patients with airway obstruction at baseline. All examinations will be carried out by a competent technician trained in obtaining the necessary cooperation from the subjects and appropriately operating the equipment in order to ensure accurate, reproducible results.

For analysis, the best forced expiratory volume after first second (FEV1) and forced vital capacity (FVC) were chosen regardless of the curve. The 'best test' curve was selected from the largest sum of FEV1 and FVC. All other lung function parameters selected for analysis were taken from the 'best test' curve. The equipment will be calibrated prior to each exam with a 3 L syringe.

ATS/ERS acceptability criteria for spirometric testing were applied, including a minimum of three respiratory manoeuvres with at least two free from artefacts. Furthermore, respiratory manoeuvres were required to show a back-extrapolated volume\5% of FVC and to meet ATS/ERS ''end of test'' criteria. Reproducibility criteria included a difference between the best and second best values for FVC and FEV1\200 ml. Diagnosis of restriction was based on an FVC below the age- and gender-adjusted predicted lower limit of normal (LLN) for FVC as defined by the ATS/ERS.[45, 47]

Definition of airway obstruction

ATS/ERS criteria served as ''reference standard'' for detection of airway obstruction.[45] The LLN was defined as age- and gender-specific fifth percentile of a healthy never-smoking population. Reference equations derived from the National Health and Nutrition Examination Study (NHANES) III were used to calculate predicted values and LLN.[48] Individuals above or below the fifth percentile were identified as normal and abnormal, respectively. Additionally, airway obstruction was calculated using the GOLD criteria (FEV1/ FVC\70%).[49] Subjects identified as normal by both cutoffs were categorized as true negatives, subjects identified abnormal by both cutoffs as true positives, subjects with an FEV1/ FVC\LLN but with FEV1/ FVC 70% as false negatives and subjects with an FEV1/ FVC the fifth percentile but FEV1/ FVC ratio\70% as false positives, respectively. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value for GOLD criteria were calculated with ATS/ERS criteria (FEV1/FVC\LLN) serving as ''reference standard''.[49]

Analysis of ventilatory muscle strength

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) constitute the most physiologically adequate tests for the determination of ventilatory muscle strength. MIP is an indicator of ventilatory capacity and the development of respiratory failure and is indicated for assessing the degree of abnormality and monitoring the weakening of inspiratory muscles individually in the progress of the disease.[50] The tests will performed in a quiet setting on the same day on which the patients undergo spirometry. The patients will be seated comfortably, with the trunk at a 90-degree angle in relation to the thighs and breathing calmly and at rest, using a nose clip. We will use two manovacuometers, an analogical aneroid RECORD (GER-AR® Comércio Produtos Médicos Ltda, São Paulo, Brazil) and another digital model, the MVD300 (Globalmed® Porto Alegre, RS, Brazil) with a pressure transducer and operating range of 0 ± 300 cm H2O.

As recommended, we will use a nozzle adapter equipped with an orifice of approximately 2 mm in diameter and 15 mm in length in order to provide an air leak and thus prevent the increase of pressure in the oral cavity generated by the undesired contraction of the muscles of the buccal wall, thereby avoiding interference in the results.[51] The digital manometer is connected to MVD300 software installed on a computer that allows viewing of graphs of sustained ventilatory muscle strength during the performance of manoeuvres effort. The MIP will be measured from the residual volume (RV), requesting a maximum inspiration from a maximal expiration, while the MEP will be verified from the total lung capacity (TLC), after the individual performs a maximal inspiration. All individuals carry out at least three reproducible manoeuvres on each of the devices supported by at least one second on analogical equipment and four seconds on digital equipment to observe the support of respiratory muscle strength. Data analysis will be computed as the value of the largest analogical, provided this does not exceed 10% over the nearest; in digital, we adopted the same procedure to register the value provided by the device (peak value), as well as the first, second, third, and fourth seconds of support obtained by extrapolating the numerical charts provided by the equipment.[52]

SLEEP EVALUATION

Epworth Sleepiness Scale

The Epworth Sleepiness Scale is a simple, self-administered questionnaire with items addressing situations involving activities of daily living and the occurrence of daytime sleepiness in adults. The subjects will be instructed to classify their likelihood of feeling the desire to nap or sleep in 8 situations on a scale of 0 to 3 (0, no chance of napping; 1, small chance of napping; 2, moderate chance of napping; and 3, strong chance of napping).[23]

Berlin Questionnaire

The Berlin questionnaire is used to identify patients at high risk of respiratory sleep disorders in a variety of populations. This clinical history questionnaire has recognised efficacy in distinguishing individuals at high risk of OSA, with 10 items organised into 3 categories as follows: snoring and apnoea (5 items), daytime sleepiness (4 items), and systemic arterial hypertension and obesity (1 item). All marked responses are considered positive. The score is divided into the following categories: category 1 is considered positive when there are 2 or more positive responses to items 1 through 5; category 2, when there are 2 or more positive responses to items 6 through 8; and category 3, when the response to item 9 is 'yes' or with BMI ³ 30 kg/m². Two or more positive categories indicate a high risk of OSA.[24]

Polysomnography

All the patients will undergo a standard overnight polysomnography (PSG) (Alice 5 Diagnostic Sleep System, Philips Healthcare, Andover (MA) USA) at the Sleep Laboratory of Nove de Julho University. PSG exams will be held the night before the haemodialysis and approximately 12h after this dialysis. All recording sensors will be attached to the patient in a non-invasive manner using tape or elastic bands. The following physiological variables will be monitored simultaneously and continuously: 4 channels for the electroencephalogram (C3-A2, C4-A1, O1-A2, and O2-A1); 2 channels for the electrooculogram (EOG-Left-A2 and EOG-Right-A1); 4 channels for the surface electromyogram (muscles of the submentonian region, anterior tibialis muscle, masseter region, and seventh intercostal space); electrocardiogram (derivation V1 modified); airflow detection via 2 channels through a thermocouple and nasal pressure cannula; respiratory effort of the thorax and abdomen via x-trace; snoring and body position sensors; and arterial oxygen saturation and heart rate via a pulse oximeter.

All the subjects will be monitored by a technician experienced in PSG. Sleep stages will be visually scored in 30 s epochs, and each PSG recording will be analysed manually under blinded conditions by one technician and one doctor with experience in scoring PSG recordings in accordance with international standards established by the Academy of Sleep Medicine Manual for Scoring Sleep and Associated Events. The patients will be instructed to remain as relaxed as possible and sleep naturally, as if at home. All signals will be recorded continuously.[53,54]

Inventory of Symptoms of Stress for Adults

Stress can be defined as any bodily reaction, together with psychological, physical, mental and hormonal components, that takes place when there is a need for adaptation to a stressful event. This reaction will be damaging if there is an extended exhibition to the event or a predisposition of the individual to certain diseases.

The Inventory of Symptoms of Stress for Adults (LIPP) is based on a 4-phase model of stress and its manifestations in the somatic and cognitive domains. In the initial stress phase, which is called the alert phase, the body makes greater efforts to prepare itself to cope with a stressor. This phase is considered a positive phase of stress because it is important for adjustments to environmental demands. The second phase is the resistance phase and occurs when a chronic stressor demands coping for a long period of time. This phase is associated with fatigue, perception of burnout, and cognitive loss. The next phases, referred to as almost exhaustion and exhaustion, are consequences of the breakdown of resistance and loss of capacity for adjustment. During these phases, one can observe important changes in sleep, work, and libido, in addition to symptoms of anxiety and depression.[25,26]

The Hospital Anxiety and Depression Scale (HAD)

The Hospital Anxiety and Depression Scale (HAD) was developed by Zigmond and Snaith[27] in 1983 to provide clinicians and scientists with a reliable, valid, and practical tool for identifying and quantifying the two most common forms of psychological disturbances in medical patients.[28] These scale is widely used as a measure of mood, emotional distress, anxiety, depression and emotional disorder in clinical populations with symptoms of physical disease. It is useful because it is quick to use and easily acceptable to patients who may be quite unwell. With only 14 items each answered on a four-point verbal rating scale, it can be used to give measures of anxiety (7 items), depression (7 items) or emotional distress (all 14 items).[29] Finally, HADS scores predict psychosocial and possibly also physical outcome.[28] The HADS was validated in Brasil through Botega et al. in 1995.[30]

Quality of Life

Stress, anxiety, and depression are common among such patients and imply a reduction in quality of life. The SF-36 will be used for the assessment of general quality of life. This measure has 36 questions grouped into 8 domains or scales of physical functioning, role limitations due to physical health, body pain, general health perception, social functioning, and role limitations due to emotional problems, vitality, and mental health.[31,32]

Myasthenia Gravis Quality of Life 15

The MG-QOL 15 is an specific questionnaire to assessment quality of life in MG patients. The MG-QOL15 has at least three potential functions. The first function patient's perception of the extent of dysfunction and degree of satisfaction or dissatisfaction with that dysfunction. A second function is to assess the course of disease and perhaps to determine the efficacy of treatment. A third function of an HRQOL measure might be to monitor aggregate HRQOLs of groups of patients to assist in determining the efficacy of a treatment.[33,34]

Myasthenia Gravis Composite Scale

The Myasthenia Gravis Composite Scale (MGC) is a reliable and valid instrument for measuring clinical status of patients with myasthenia gravis in the practice setting and in clinical trials. The validity and reliability were previously demonstrated using conventional psychometric tests. The MGC scale consists of test items that measure symptoms and signs of MG, with weighted response options.[35,36] The MGC takes less than five minutes to complete. It is made up of three ocular (if one classifies eye closure as ocular), three bulbar, one respiratory, one neck, and two limb items.[37]

Quantitative Myasthenia Gravis Score

The Quantitative Myasthenia Gravis Score (QMGS) is a commonly used outcome measure in MG. It was first developed by Besinger in 1983 as an outcome measure for a clinical trial. Basinger et al introduced a clinical scoring system to assess the degree of disease severity in MG patients. Their system consisted of 8 items and was later expanded by Barohn to 13 items, each with a possible score from 0 to 3, and a maximum possible of 39 points, where a higher score indicated more severe disease.[38,40] Barnett et al demonstrate that the QMGS is a valid marker for disease severity supporting the use of the QMGS as a primary outcome measure in a clinical trials of MG.[39]

Quality control

To ensure the quality of the data, the physiotherapists and physicians in charge of data collection will receive specific training. Periodic external monitoring will be performed to verify the adequate application of methodology in performing examinations and data collection.

DISCUSSION

Despite the existence of scientific evidence, OSA is still underdiagnosed in the general population. This is probably due to several causes, such as lack of knowledge among health professionals and also due to the limited patient access to diagnosis and treatment. In addition, the diagnostic procedures are expensive and predictive criteria still unsatisfactory.[55,56]

Myasthenia gravis is an autoimmune disease characterized by the development of autoantibodies against

the acetylcholine receptors of the neuromuscular junction and subsequent reduction in the quantity of available receptors. Unfortunately, therapies for MG do not always produce a complete remission of the disease, so clinical activity may significantly decrease quality of life.[57] The data on sleep-related disorders and sleep quality in MG are scarce and inconclusive. Few studies were conducted through standard overnight polysomnography, and still controversial in relation to prevalence and classification of sleep breathing disorders.

OSA is a respiratory disease characterized by the collapse of the upper airways which occurs during sleep in predisposed subjects. There is a close relationship between OSA and the risk of cardiovascular disease[58,59], neuropsychological problems[60], reduction in quality of life[61,12] and increase in the use of health resources[13,14], demonstrating that, when underdiagnosed, OSA can have serious consequences. Thus, the identification of new markers for OSA can be of considerable relevance for clinical practice. Investigators have identified anatomical factors[17-19], neuromuscular control factors[20,21] and liquid and fat deposits[21] that may lead to increased pharyngeal collapsibility during sleep.

This study will allow the use of new screening technique to detect upper airway collapsibility, a high risk indicator for OSA in MG patients. It's a daytime, low-cost method that could be included in a preventive strategy aimed at reducing the impact of this condition on development of cardiovascular consequences.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS CONTRIBUTION

All the authors contributed to the conception and design the study. LVFO, SRN, EFO, and ASB provided the idea for the study, established the hypothesis and wrote the original proposal. NA, LMF, AKFA, SRN, LVFO, VCL, ASB, GI, SR, EFO, NTF, JJU, PCB, IRS, EAPS, FSSLS and ISD will participate in the conduct with clinical screening tests, application of psychological instruments, and data analysis. LVFO, SRN, EFO, FSSLF, VCL, ASB, JCFC, FIC, PCB, and LMMS significantly contributed to writing this paper, while IRS, JJU, ISD, RGA, NTF, JCFC, SR, AS, AB, CSO and GI were involved in critically revising the manuscript. This protocol paper was written by LVFO, SRN, and ASB with input from all co-authors. All authors read and approved the final manuscript.

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