Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

The impact of aerobic exercise on fatigue, kinesiophobia and disease severity in myasthenia gravis patients

Ozgur Zeliha Karaahmet[a], Eda Gurcay[b], Fatma Balli Uz[a], Yasemin Tombak[a,*], Mehlika Panpalli Ates[c], Savas Altinsoy[d]

[a] *University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Physical Medicine Rehabilitation, Ankara, Turkey*
[b] *University of Health Sciences, Gaziler Physical Therapy and Rehabilitation Training and Research Hospital, Department of Physical Medicine Rehabilitation, Ankara, Turkey*
[c] *University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Neurology, Ankara, Turkey*
[d] *University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Anesthesiology and Reanimation, Ankara, Turkey*

ARTICLE INFO

Keywords:
Myasthenia gravis
Aerobic exercise
Fatigue
Kinesiophobia
Ergospirometric cardiopulmonary stress test

Received: Dec 08, 2021
Accepted: Feb 14, 2022
Available Online: May XX, 2022

DOI:
10.5455/annalsmedres.2021.09.563

Abstract

Aim: To determine the aerobic capacity of generalized myasthenia gravis (MG) cases and to explore the effect of aerobic exercise on maximum aerobic capacity, fatigue level, kinesiophobia, and disease severity parameters.

Materials and Methods: The seropositive-confirmed generalized MG cases who were between the ages of 18 and 80 years and between 2-4 stages, at the same time hospitalized in the physical therapy and rehabilitation clinic for three weeks were included in this study. Outcome measures of the 6-minute walk test (6MWT), the ergospirometric cardiopulmonary stress test (ETT), the multidimensional fatigue scale (MFS), the Quantitative Myasthenia Gravis Score (QMG) and, the Tampa kinesophobia scale (TKS) were evaluated at admission and discharge.

Results: A negative correlation between VO2 max and kinesophobia and fatigue (p= 0.020, r= -0.750; p= 0.031, r= -0.714, respectively) was determined, while a positive correlation was recorded between VO2 max and 6-MWT (r= 0.783 p= 0.013).

Conclusion: Intermittent aerobic exercise programs can be safely administered under supervision in generalized MG patients. The functional capacity of the patients increased, fatigue and fear of movement decreased.

Registration: The Ethics Committee in the University of Health Sciences, Diskapi Training and Research Hospital confirmed the study (Protocol #91/05 Dated 06.07.2020).

Introduction

Myasthenia gravis (MG) is an immune system disease designated by a lack of power and lassitude of skeletal muscles. The weakness is the consequence of an antibody and T-cell-related immunological invasion conducted at proteins in -associated proteins. MG can be defined by clinical and serologic tests [1, 2]. The patients have characteristically floating weakness and fatigue at the specific muscle groups influenced [2]. Generally, the weakness may float during the day however is mostly worse late in the day, or after exercise. At the onset of the disease, symptoms may not be present in the morning. When the disease proceeds, asymptomatic periods clear away; symptoms are frequently present but fluctuate from mild to severe. There are four major therapy for MG; anticholinesterase agents, immunomodulatory drugs, immunosuppressive agents, and thymectomy [3]. Since most MG patients have residual signs and deficiencies considering ideal treatment, interventions that can resist these signs are highly assured [4]. Additionally, MG patients have a high prevalence of depression with lower than the normal health-related quality of life values, and strain in carrying out activities of daily living. Fallen aerobic capacity has also been recorded in patients with generalized MG [5, 6].

Low or medium-intensity physical activity and systematic training programs have been recommended for MG patients in addition to drug therapy [7], however, there are

*Corresponding author:
Email address: yasemintombak@hotmail.com (Yasemin Tombak)

not enough studies on how aerobic exercise affects the disease or the issues that should be considered when exercise training is recommended.

Many patients with MG have antibodies against the muscle nicotinic acetylcholine receptor (AChR). MG is a T cell-dependent, B cell-mediated disease.

Animal studies have indicated that tumor necrosis factor-alpha (TNF-alpha) acts a significant role in the pathogenesis of MG, and essays of monoclonal antibodies that block TNF-alpha maintain clinical amelioration [8].

It was found that there is a decrease in TNF-α release in skeletal muscle with exercise training. Besides, early exercise is mostly pro-inflammatory with an evident rise in cytokine levels. Prolonged physical activity decreases the autoimmune reply [9].

In the light of all this information, it is considered that long-term, aerobic exercise might contribute to disease control in MG patients. Therefore, this study is conducted to determine the aerobic capacity of patients with MG and to examine the impact of aerobic exercise on the maximal aerobic capacity, fatigue levels, kinesiophobia, and disease severity parameters.

Materials and Methods

Study design

Cases with MG who were forwarded by the neurology clinic and hospitalized in the Physical Medicine and Rehabilitation Clinic were taken in the study. The study approval was obtained from the local ethics committee (Diskapi Yildirim Beyazit Education and Research Hospital Ethics Committee, Protocol #91/05, Dated 06.07.2020) and the study was conducted by the Declaration of Helsinki.

Participants

Patients between the ages of 18 and 80 years, with a seropositive-confirmed generalized MG (Myasthenia Gravis Foundation of America (MGFA) classification) [10] who were between 2-4 stages were eligible for the study. Patients who had cardiorespiratory, orthopedic, or metabolic comorbidities, dementia, and pregnancy were excluded from the study.

Evaluation parameters

Demographic characteristics concerning age, gender, BMI, marital, employment, and smoking status, disease duration, family history, comorbidities (Hypertension, Diabetes Mellitus, Coronary Artery Disease), and drugs usage were recorded at initial evaluation.

Outcome measures were conducted at admission and discharge.

The ergospirometric cardiopulmonary stress test (ETT), the 6-minute walk test (6MWT) [11], the multidimensional fatigue scale (MFS) [12, 13), and the Tampa kinesophobia scale (TKS) [14) were applied as functional measurements.

Fatigue level was scored using the Turkish version of the MFS which contains 16 items and four dimensions of fatigue; severity, distress, degree of interference in activities of daily living, and timing.

Fear of movement was scored using the Turkish version of the TKS. The scale includes injury / re-injury and fear-avoidance parameters. It is created of 17 questions with a 4-point Likert scale (from strongly disagree to strongly agree). After reversing the 4, 8, 12, and 16 items, the total score is calculated. It is scored between 17 and 68. The higher the score indicates the higher the kinesophobia.

The MGFA classification and the Quantitative Myasthenia Gravis Score (QMG) [15) were used for clinical evaluation. The classification of the MGFA was planned to identify subgroups of patients with MG who are diverse from each other with their clinical features or severity of the disease. According to the MGFA classification, patients are grouped into ocular (MGFA I) or generalized (MGFA II-IV) MG patients. The generalized MG is divided into muscle weakness predominantly affecting limb and/or axial muscles (MGFA II-IVa) and muscle disease predominantly affecting oropharyngeal and/or respiratory muscles (MGFA III-Vb). Disease severity was evaluated using the QMG score. The QMG score was evolved as a tool for assessing disease severity. The score enables to test of the deficits based on quantitative testing of guard muscle groups. It is a 13-item scale with scores ranging from 0 to 39, with higher *scores* remarking more severe disease.

Exercise program

The aerobic exercise program prescribed according to the VO2 max value found in the exercise tolerance test (ETT) was applied. According to the calculated speed, the program was planned as 5 days a week and 20-30 minutes a day. Before the aerobic exercise, the patients were given 10 minutes of warm-up and breathing exercises. Light strengthening, posture, and balance exercises were also added to aerobic exercises during the day.

Data analysis

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of distribution was evaluated by the Shapiro Wilk test. Descriptive statistics are served as mean ± standard deviation for continuous variables, and as a percentage for categorical variables. Wilcoxon tests were used to evaluate whether the variations between the repetitive measurements were significant or not. Pearson's correlation coefficient was used to describe the correlations. Those with a $p < 0.05$ were accepted as statistically significant.

Results

A total of 9 patients with generalized MG were included in this study. Demographic and clinical characteristics of the patients are presented in Tables 1 and 2.

No complications were recorded during the exercise test and exercise training. The changes in ETT and clinical parameters before and after the treatment is are illustrated in Table 3.

No correlation was found between age and kinesophobia, fatigue, and VO2 max (p= 0.246, r= -0.431; p= 0.758, r= -0.120; p= 0.933, r= 0.033, respectively). Likewise,

Table 1. Demographic characteristics of the patients

	n (%) / mean ± (SD)
Age, years	54.5±12
Gender, female	9 (100)
Disease duration, months	75.5±78.3
Seropositive	3 (33)
Steroid and/or DMARD use	5 (56)
Pyridostigmine use	9 (100)

Table 2. Clinical characteristics of the patients

	n (%)
Thymectomy	5 (56)
Myasthenic crisis	1(11)
Cholinergic crisis	0
Pain	9 (100)
Sleep disturbance	9 (100)
Dysphagia	6 (67)

there was no correlation between disease duration and kinesophobia, fatigue, and VO2 max (p= 0.740, r= -0.129; p= 0.390, r= -0.327; p= 0.957, r= 0.021, respectively). A negative correlation between VO2 max and kinesophobia and fatigue (p= 0.020, r= -0.750; p= 0.031, r= -0.714, respectively) was determined, while a positive correlation was recorded between VO2 max and 6-MWT (r= 0.783 p= 0.013).

Discussion

This study was conducted to define the aerobic capacity of patients with MG and to examine the effect of the aerobic exercise program on the patients' maximal aerobic capacity, fatigue levels, fear of movement, and disease severity parameters. The aerobic exercise program was applied to the patients for 3 weeks, 5 days a week. As a result, patients' functional capacity increased, fatigue and fear of movement decreased.

MG is a rare disease with an annual incidence of about 7 to 23 new cases per million. MG can begin at any age but bears to be a bimodal distribution to the age of onset with an early peak in the second and third decades with female predominance [16]. In the current study, all patients were female and the mean age was 54 years.

The best indicator of cardiorespiratory endurance is VO2 max, which is the maximal amount of oxygen consumed by the human body per minute during heavy physical activities. While skeletal muscle receives 4-5 ml of oxygen from 100 ml of blood during rest, it receives 15-17 ml of oxygen during maximal exercise. The highest amount of oxygen that a person can use per unit time during exercise is expressed as maximal oxygen use (VO2 max) and is the best indicator of maximal aerobic power. In women, VO2 max norms have been defined in 7 levels ranging from very poor to excellent according to the ages [17]. The mean age of our patient group was 54.5 ± 12 years and the mean VO2 max was 14.2 ± 4 at a very poor level according to this scale.

In our study, patients with high fatigue and kinesiophobia scores showed a negative correlation in terms of VO2 max values. As a result, while kinesiophobia and fatigue scores decreased with aerobic exercise, VO2 max values increased. Similar to our study, two studies, one of which was conducted with 10 and the other 12 patients to investigate whether exercise can be applied safely in MG, be safe, and provide positive results in neuromuscular parameters [18, 19].

Table 3. The changes in ETT and clinical paramteres before and after the treatment

	Before treatmentmean ± SD	After treatmentmean ± SD	p
6-MWT (m)	335±58	370±80	0.173
VO2 max (ml/kg/min)	14.2±4	16.6±4	0.012
MET	4±1.1	4.7±1.1	0.012
Load (watt)	78.6±62	105.4±78.5	0.018
Tiredness	54.1±4.8	49.3±5.6	0.043
TKS	49.4±8.4	45.4±5.7	0.012
QMG	4.1±1	3.5±0.8	0.059

ETT, exercise tolerance test; 6-MWT, 6-minute walk test; MET, Metabolic Equivalent Minute; TKS, Tampa kinesophobia scale; QMG, Quantitative Myasthenia Gravis score

There were no studies on risk factors that may occur during exercise training in MG patients. However, in a case report of a 36-year-old female marathon runner with MG, it was determined that ocular, bulbar, and localized limb fatigue was present, but more than one marathon was completed with cholinesterase inhibitors and disease stability was provided [20]. In our study, no complications occurred during ETT or exercise training, and patients did not have to discontinue the treatment.

The limitations of our study are the relatively small number of patients and the lack of a control group. The reason for this is that only patients with neurological deficits can be admitted to the rehabilitation clinic due to the limited bed capacity. The nine female patients diagnosed with generalized MG were admitted to our clinic due to reasons such as not being able to benefit from the drugs adequately and continuing severe fatigue complaints.

MG is a neuromuscular disease with the most important symptom of muscle fatigue. However, there is very limited scientific-based information on how aerobic exercise affects the disease or the existence of issues to consider when recommending exercise training. Our study has demonstrated the relationship between low VO2 max and fatigue and kinesophobia, and this will lead to a vicious circle. Aerobic exercise is emerging as a safe and non-pharmacological treatment alternative to reduce the symptoms of these patients.

In conclusion, an aerobic exercise program with intervals could be applied safely under supervision in patients with generalized MG. Patients' functional capacity increased, fatigue and fear of movement decreased.

Declarations

Ethics approval

The study protocol received institutional review board approval and all participants provided informed consent in the format required by the clinical research ethics committee of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital.

References

1. Silvestri NJ, Wolfe GI. Myasthenia Gravis. Semin Neurol. 2012;32:215.
2. Keesey JC. Clinical evaluation and management of myasthenia gravis. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2004;29(4):484-505.
3. Jones, L.A., Robertson, N.P. An update on treatments in myasthenia gravis. J Neurol. 2017;264:205–207.
4. Schepelmann K, Winter Y, Spottke AE, Claus D, Grothe C, Schröder R, et al. Socioeconomic burden of amyotrophic lateral sclerosis, myasthenia gravis and facioscapulohumeral muscular dystrophy. J Neurol. 2010;257:15-23.
5. Twork S, Wiesmeth S, Klewer J, Pöhlau D, Kugler J. Quality of life and life circumstances in German myasthenia gravis patients. Health Qual Life Outcomes. 2010;8:129.
6. Leonardi M, Raggi A, Antozzi C, Confalonieri P, Maggi L, Cornelio F, et al.
7. Disability and functional profiles of patients with myasthenia gravis measured with ICF classification. Int J Rehabil Res. 2009;32:167-72.
8. Nils E. Gilhus. Myasthenia Gravis. N Engl J Med. 2016;375:2570-81.
9. Lee JS, Jook IS, Seok JI. Widely varying TNF-alpha levels in patients with myasthenia gravis. Neurol Sci. 2009;30:259-62.
10. Suzuki K. Cytokine Response to Exercise and Its Modulation. Antioxidants. 2018;7:17.
11. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016;87(4):419-25.
12. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J. 1985 Apr 15;132(8):919-23.
13. Yildirim Y, Ergin G. A Validity and reliability study of the Turkish Multidimensional Assessment of Fatigue (MAF) scale in chronic musculoskeletal physical therapy patients. Back Musculoskelet Rehabil. 2013;26:307-16.
14. Tunca Yılmaz O., Yakut Y., Uygur F. ve Ulug N. Tampa Kinezyofobi Olcegi'nin Turkce Versiyonu ve Test Tekrar Test Guvenirligi. Fizyoterapi Rehabilitasyon Dergisi 2011;22:44-9.
15. Jaretzki 3rd A, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 2000;55:16-23.
16. Sharshar T, Chevret S, Mazighi M, Chillet P, Huberfeld G, Berreotta C, et al. Validity and reliability of two muscle strength scores commonly used as endpoints in assessing treatment of myasthenia gravis. J Neurol. 2000;247(4):286–90.
17. Breiner A, Widdifield J, Katzberg HD et al. Epidemiology of myasthenia gravis in Ontario, Canada. Neuromuscular Disord. 2016;26:41
18. Heyward, V. Advanced Fitness Assessment & Exercise Prescription (3rd Ed). Champaign, IL: Human Kinetics, 1997.
19. Rahbek MA, Mikkelsen EE, Overgaard K, Vinge L, Andersen H, Dalgas U. Exercise in Myasthenia Gravis: A Feasibility Study of Aerobic and Resistance Training. Muscle Nerve. 2017;56:700-9.
20. Westerberg E, Molin CJ, Lindblad I, Emtner M, Punga AR. Physical Exercise in Myasthenia Gravis Is Safe and Improves Neuromuscular Parameters and Physical Performance-Based Measures: A Pilot Study. Muscle Nerve. 2017;56:207-14.
21. Birnbaum S, Sharshar T, Eymard B, Theaudin M, Portero P, Hogrel JY. Marathons and myasthenia gravis: a case report. BMC Neurol. 2018;18:145.