MYASTHENIA GRAVIS WITH EXERCISE INTOLERANCE, LOW CARDIORESPIRATORY AND MUSCLE ENDURANCE

Tresia Fransiska Ulianna Tambunan, Carissa Putri Crisdayani
Physical Medicine and Rehabilitation Department, Faculty of Medicine Universitas Indonesia,
Cipto Mangunkusumo Hospital, Indonesia

ABSTRACT

Introduction: Myasthenia Gravis (MG) is a relatively rare autoimmune disorder caused by an antibody-mediated blockage of neuromuscular transmission resulting in a skeletal muscle weakness and rapid muscle fatigue. Muscular weakness in MG can affect ocular, limb, respiratory, and bulbar muscles, which varies over time and is often activity or exercise induced. **Case Illustration:** A 28-year-old man with easily fatigued when performing working activities as an anesthesiology resident such as manual bagging, intubation, and cardiopulmonary resuscitation. Patient was diagnosed with MG with dominant symptoms which are hand tremors and fatigue. From physical examination, we found fair left hand grip strength, relatively similar dexterity on both hands, exercise intolerance, low cardiorespiratory and muscle endurance. Laboratory examination showed negative antibodies for MG. Radiology findings showed that he had no abnormalities. The patient did several physical exercises given by physiatrist, such as aerobic exercise, upper extremity resistance exercise, task-spesific exercise, and core muscle exercise. **Discussion:** Exercise capacity in MG may be restricted by proximal muscle weakness, fatigability, and impairment in respiratory muscle function. Physical exercise leads to an immune response, with a rise in T regulatory cells, decreased immunoglobulin secretion, and a shift in the Th1/Th2 balance towards a decreased Th1 cell production. Beneficial effects of physical activity are improvements in mood, reduction in fatigue, and positive effects on cognition and mobility. **Conclusion:** Physical exercise such as aerobic exercise and resistance training on upper extremities are proven to reduce fatigue and hand tremors, and also improve the quality of life of MG patients.

Keywords: myasthenia gravis, physical exercise

ABSTRAK

Pendahuluan: Myasthenia gravis adalah penyakit autoimun yang cukup jarang ditemukan. Penyakit ini disebabkan oleh penutupan neuromuscular transmission sehungga menyebabkan kelemahan otot skeletal dan fatigue otot secara cepat. Kelamahan otot dapat terjadi pada otot okuler, ekstremitas, otot pernapasan, dan otot bulbar yang dapat bervariasi dalam waktu dan diperparah dengan adanya aktivitas. Ilustrasi **Kasus:** seorang laki-laki, 28 tahun, memiliki keluhan mudah lelah saat melakukan aktivitas yang berhubungan dengan pekerjaannya sebagai residen anestesi yaitu melakukan intubasi dan resusitasi. Pasien didiagnosis sebagai MG dengan gejala utama berupa tremor pada tangan dan adanya fatigue. Pemerikaan fisik menunjukkan adanya penurunan kekuatan genggam tangan kiri, ketangkasan kedua tangan relatif sama, intoleransi latihan, endurance kardiorespirasi dan otot yang rendah. Pemeriksaan laboratorium menunjukkan antibodi negatif terhadap MG. Pemerikaan radiologis menunjukkan tidak ada kelainan. Pasien melakukan berbagai latihan fisik yang diresepkan olek dokter spesialis kedokteran fisik dan rehabilitasi seperti latihan aerobik, latihan resistensi ekstremitas atas, task specific exercise, dan latihan otot core. **Diskusi:** Kapasitas latihan seseorang dengan MG dibatasi oleh adanya kelemahan otot proksimal, fatigue, dan gangguan pada fungsi otot respirasi. Latihan fisik menimbulkan respon imun, meningkatkan sel T regulatori, menurunkan sekresi immunoglobulin, dan pergeseran keseimbangan Th1/Th2 yang menyebabkan penurunan produksi Th1. Manfaat aktvitas fisik adalah dapat memperbaiki mood, mengurangi fatigue, dam memberikan efek positif pada kognisis dan mobilitas Kesimpulan: Latihan fisik seperti latihan aerobik dan latihan resistensi pada ekstremitas atas terbukti dapat mengurangi fatigue dan tremor tangan, serta dapat meningkatkan kualitas hidup pasien MG

Kata kunci: myasthenia gravis, latihan fisik

Correspondence :
Tresia Fransiska Tambunan, Carissa Putri Crisdayani
Physical Medicine and Rehabilitation Department,
Faculty of Medicine Universitas Indonesia,
Cipto Mangunkusumo Hospital, Indonesia
Email : ina.j.chest@gmail.com

How to cite this article :
MYASTHENIA GRAVIS WITH EXERCISE INTOLERANCE, LOW CARDIORESPIRATORY AND MUSCLE ENDURANCE

INTRODUCTION

Myasthenia gravis (MG) is a relatively rare autoimmune disorder caused by an antibody-mediated blockage of neuromuscular transmission resulting in a skeletal muscle weakness and rapid muscle fatigue. Muscular weakness in MG can affect ocular, limb, respiratory, and bulbar muscles, which varies over time, and is often activity or exercise induced.[1] The neuromuscular transmission "safety factor" is reduced in MG patients. Reduction in number or activity of the acetylcholine receptors (AChR) molecules at the neuromuscular junctions (NMJ) decreases the end-plate potential (EPP), which may be adequate at rest; but when the quantal release of acetylcholine is reduced after repetitive activity, the EPP may fall below the threshold needed to trigger the action potential. This translates as a clinical muscle weakness, and when EPP, at rest is consistently below the action potential threshold, it leads to a persistent weakness. Therapy for MG should be tailor made according to the underlying etiology of MG in each patient. During the last decade, the provision of exercise therapy has become the reason for additional therapy with the aim of reducing symptoms and to improve the patient's quality of life.[2]

CASE ILLUSTRATION

A 28-year-old man experienced becoming easily fatigued and droopy eyes since February 2020. Initially, he thought he was exhausted from work, so he did not seek any medical advice. On September 2020, he had COVID-19 infection with mild symptoms. After that, he noticed that fatigue and droopy eyes become more severe. He went to neurologist on November 2020 and underwent several examinations, later diagnosed with Myasthenia Gravis Seronegative. By this time, he was having difficulties when handling laryngoscope during anesthesia procedure especially at night times due to hand tremors. Fatigue was relieved by resting for 20 minutes, but the hand tremors took longer to be resolved. As time went on, the symptoms got worse and he had to take a temporary leave on January to July 2021.

The patient was consulted to the Physical Medicine and Rehabilitation Department on February 2021 and had undergone occupational therapy to improve hand function for 5 months. At this time, he became easily fatigued when he walked for about 30 minutes.

By July 2021, Anesthesiology Department requested a Functional Capacity Evaluation (FCE) to determine his capacity to perform work activities during residency. The FCE recommended that currently he was unable to perform his duties as an anesthesiology resident. From the FCE we found that he could not achieve required basic skills in anesthesia procedure, such as manual bagging, intubation and cardiopulmonary resuscitation (CPR). Also, he had not met the required fitness level to perform his work activities which causes a high fatigue level. Working in high fatigue level might lower the patient's thinking ability, concentration and increase the chance of human error during working activities. Based on the FCE recommendation, he needs cardiorespiratory rehabilitation program in order to improve his fitness level before returning to his residency.

Currently, he is working on trial in the Anesthesiology Department for 8 hours under supervision. He is able to perform manual bagging for 3 minutes, laryngoscope handling for 3 minutes and CPR for 1 minute before experiencing fatigue. He still experienced fatigue whenever walking during working hours, especially at a brisk walking pace. His functional capacity will be re-evaluated by December 2021.

From the nutritional status, his body weight was 86 kg, body height was 170 cm, and body mass index was 29,7 kg/cm^2 (obesity grade I). From physical examination, we found the right-hand grip strength was 12-17 kg and the left-hand grip strength was 6-10 kg. Dexterity test (peg board hole test) was

relatively similar both hands with 22 second on right hand and 23 second on left hand. The cylindrical grasp, spherical grasp, tip to tip, lateral pinch, three jaw chuck was adequate on both hands. The total distance of the 6-minutes walking test was 442 meters, with a predicted maximum oxygen uptake (VO_2max) of 16,1 L/min equal to 4,6 metabolic equivalent (METs). From the FCE, we asked the patients to do specific tasks on a dummy, such as manual bagging, intubation and CPR. When patient performed the manual bagging with left-hand, he felt pain and tremors, after 3 minutes and 15 seconds. He also felt pain and tremors performing manual bagging with right hand, after 3 minutes and 15 seconds. After a rest for 10 minutes and 30 minutes, he was unable to continue due to tremors on the entire left arm. He was able to complete the intubation procedure in 20 seconds and felt tremors on left-hand occur after the procedure. He was able to perform CPR with the correct maneuver for 1 minute and 25 seconds and stopped due to muscle tenderness on the hypogastric region. He was able to maintain jaw thrust position while doing manual bagging for 3 minutes. The fatigue severity score was 37.

Figure 1. Patient's Posture

Laboratory Findings

	Normal value	Unit	
Hemoglobin	13,0 – 17,0	g/dL	16,7
Hematocrit	40,0 – 50,0	%	44,7
Leukocytes	4,0 – 10,0	10^3/µL	4,62
Thrombocyte	150 – 410	10^3/µL	218
Count Type:			
Basophil	0 – 2	%	0,6
Eosinophil	1,0 – 6,0	%	4,1
Neutrophil	40 - 80	%	44
Lymphocyte	20 - 40	%	2,7
Monocyte	2,0 – 10,0	%	4,4
Neutrophil count	1,70 – 7,50	10^3/µL	40,1

Lymphocyte count	1,0 – 3,2	10^3/µL	10,5
Urea	19 – 44	mg/dL	24,1
Creatinine	0,73 – 1,18	mg/dL	0,7

Anti-AChr antibody : negative

Anti-MUSK antibody : negative

The medical diagnosis of this patient was MG, obesity grade I, and a history of COVID-19 infection. The problems encountered during rehabilitation were exercise intolerance, low muscle endurance of upper extremity, low cardiorespiratory endurance, fatigue, and occupational disability.

To improve the exercise tolerance, cardiorespiratory endurance, and to achieve and maintain normo-weight the patient was given aerobic exercise with treadmill, moderate intensity 50-60% heart rate reserve (HRR) 136-147 bpm, with incremental: first 15" speed 6,1 km/h, inclination level 1,5%; second 15" speed 5,6 km/h, inclination level 1%; for total 30 minutes, 1 time a week and home program was walking for 30 minutes, target heart rate 50-60% 3x/week.
To improve muscle endurance of upper extremity, he was given unsupported arm exercise using a resistance band, 3 sets 8 repetition, 3 times a week (different day with aerobic exercise). To improve task-specific exercise, he was given intubation procedure exercise 5 repetition, hold for 5 seconds and incremental hand movement (full fist, hook, straight fist, duck, finger spread with resistance) 15-25 repetition. To improve core muscle strength, he was given plank exercise 3x/week, with increasing duration as tolerated.

After 8 weeks of training, the patient felt reduced fatigue during working hours, can perform manual bagging for 5 minutes without hand tremors. Increased walking distance for 520,8 m and increased predicted VO_2max: 17,3 L/min. The fatigue severity score was decreased to 32.

DISCUSSION

Myasthenia gravis (MG) is a relatively rare acquired, autoimmune disorder caused by an antibody-mediated blockage of neuromuscular transmission resulting in skeletal muscle weakness and rapid muscle fatigue. Muscular weakness in MG can affect ocular, limb, respiratory, and bulbar muscles, which varies over time and is often activity or exercise induced.[1,3]

Exercise capacity in MG may be restricted by proximal muscle weakness, fatigability, and impairment in respiratory muscle function.[4] Furthermore, the inherent muscle weakness and the subsequent risk of increased sedentary behavior in MG may in turn increase the risk of becoming overweight, developing respiratory infections, and osteoporosis, which potentially leads to falls and fractures. Poor physical fitness in healthy individuals as well as MG patients may result in a "vicious circle" where physical deconditioning causes lethargy and fatigue and in younger individuals, non-specific fatigue disorders, which are part of the differential diagnosis for MG.[5]

Physical exercise leads to an immune response, with a rise in T regulatory cells, decreased immunoglobulin secretion, and a shift in the Th1/Th2 balance toward decreased Th1 cell production. In addition, physical exercise causes release of the myokine (cytokine released by skeletal muscle) IL-6, which induces an anti-inflammatory response through IL10 secretion and IL-1β inhibition. Additional beneficial effects of physical activity are improvements in mood, reduction in fatigue, and positive effects on cognition and mobility, seen for example in patients with multiple sclerosis. Furthermore,

physical activity improves QoL and reduces co-morbid cardiovascular disorders in SLE and RA patients.[6]

General fatigue and cardiovascular deconditioning are more prevalent amongst patients with neuromuscular diseases compared with the general population. Regarding neuromuscular disorders in general, few well-designed studies have been conducted on the benefits or disadvantages of physical exercise. In inflammatory muscle diseases, including polymyositis and dermatomyositis, exercise enhances aerobic capacity, improves muscle function, and reduces disabilities. In patients with inflammatory polyneuropathy, significant improvement in muscle resistance, functional activities, and physiological adaptations following exercise are reported. In addition, reduction in chronic fatigue has been reported in patients with facioscapulohumeral muscular dystrophy type 1.[7]

A detailed review on exercise in relation to a broad spectrum of neuromuscular diseases, concluded that a regular exercise regimen is beneficial against neuromuscular disease, whether it is aerobic/endurance or strength/resistance training. It is recommended that patients should establish an exercise program with their physician and that those with neuromuscular junction disorders and metabolic myopathies should combine strength training and submaximal aerobic exercise on alternating days (though it is unclear exactly what evidence this was based on), aim to slowly increase the number of repetitions and achieve 65% of maximal heart rate (220-age/min) during aerobic training.[8]

The patient was prescribed with aerobic exercise, with a target heart rate 50-60% using a hospital-based treadmill once a week and walking for 30 minutes with the same target heart rate for a home-program 3 days aweek. Other than that, he was also prescribed an upper extremity endurance training specific tasks, as well as core training every other day. After following the rehabilitation program, he had improvement in hand endurance function and cardiorespiratory endurance as well as exercise tolerance. Currently he is in trial on his residency program. He felt that he is less fatigue while working, able to do manual bagging for more than 5 minutes before tremors, perform an intubation, but he still has not performed CPR yet in the meantime. He is able to stand for 1 hour before needing rest. When fatigue or tremors occur, he needs 5 minutes of rest before the fatigue reduces, and 20 minutes until no fatigue remains is felt.

CONCLUSION

Physical exercise such as aerobic exercise, resistance training, and upper extremity muscles endurance training are proven to reduce fatigue and hand tremors, while also improving the quality of life of MG patients.

REFERENCES

1. Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: A review. Vol. 1, Autoimmune Diseases. 2012.
2. O'Connor L, Westerberg E, Punga AR. Myasthenia Gravis and Physical Exercise: A Novel Paradigm. Front Neurol. 2020;11:1–12.
3. Havlícek F. Myasthenia gravis. Cas Lek Cesk. 1981;120:1073–7.
4. Elsais A, Johansen B, Kerty E. Airway limitation and exercise intolerance in well-regulated myasthenia gravis patients. Acta Neurol Scand. 2010;122:12–7.
5. Abresch RT, Han JJ, Carter GT. Rehabilitation management of neuromuscular disease: The role of exercise training. J Clin Neuromuscul Dis. 2009;11:7–21.
6. Shao T, Verma HK, Pande B, Costanzo V, Ye W, Cai Y, et al. Physical Activity and Nutritional Influence on Immune Function: An Important Strategy to Improve

Immunity and Health Status. Front Physiol. 2021;12.
7. Westerberg E, Molin CJ, Nees SS, Widenfalk J, Punga AR. The impact of physical exercise on neuromuscular function in Myasthenia gravis patients: A single-subject design study. Med (United States). 2018;97.
8. 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 and Nerve. 2017;56:207–14.