Cross-Sectional Study

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Correlation of fatigue on walking ability in myasthenia gravis patients: a cross-sectional study

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Introduction: Myasthenia gravis (MG) is a neuromuscular junction autoimmune disease characterised of intermittent muscle weakness that increases with activity and recovers with rest.
Objective: Analysing the correlation of fatigue on walking ability in MG patients.
Methods: This study used a cross-sectional design with consecutive sampling. Participants MG patients took in this trial. Data collection encompasses fatigue and walking ability, with fatigue being assessed using the fatigue severity scale (FSS) and walking ability being assessed using the 10-metre walking test. The 10-metre walking test assessment contains three components: comfortable walking speed (CWS), maximum walking speed (MWS), and natural cadence. The statistical analysis used in this study includes the Pearson correlation and Spearman rank tests with $P < 0.05$.
Results: The number of participants was 23 MG patients, and most of the participant was female (69.6%). The participant's fatigue value was 5.46 ± 1.13, including MGFA 1 = 5.32 ± 1.15, MGFA 2A = 5.5 ± 1.11, and MGFA 2B = 5.61 ± 1.30. Meanwhile, the participant's walking abilities included CWS of 1.10 ± 0.11 m/s, MWS of 1.31 ± 0.15 m/s, and natural cadence of 110.91 ± 7.74 steps/min. No significant correlation of fatigue on walking ability including FSS vs. CWS ($r = -0.141$; $P = 0.520$), FSS vs MWS ($r = -0.169$; $P = 0.442$), and FSS vs. natural cadence ($r = -0.050$; $P = 0.822$).
Conclusion: There was no significant correlation between fatigue and walking ability in MG patients who had MGFA 1, MGFA 2A, and MGFA 2B.

Keywords: fatigue, healthy lifestyle, myasthenia gravis, walking ability

Introduction

Myasthenia gravis (MG) is a neurological autoimmune disease characterised by the deposition of auto-antibody at the neuromuscular junction[1]. Since the early twentieth century, the mortality rate of MG has been dramatically lowered after the discovery of acetylcholine esterase inhibitors, immunosuppressants, intravenous immunoglobulin and more advanced breathing apparatus. Previous study data showed that the mortality rate reached 2.2%, with elderly age and respiratory failure being the leading reasons of death[2]. Despite the fact that medication has been shown to improve the clinical condition of MG patients, some patients continue to complain of weakness and fatigue, resulting in a lower quality of life[3].

HIGHLIGHTS

- No significant correlation found between fatigue and walking ability.
- In terms of fatigue and freshness, myasthenia gravis (MG) patient's walking abilities were comparable.
- No significant correlation of fatigue found on comfortable walking speed, maximum walking speed, and natural cadence in myasthenia gravis patients.

The incidence and prevalence rates of MG differ by region. However, the global incidence rate has risen during the last 7 decades[2]. The rise in the number of MG cases can be attributed to improved diagnostic and incentivized treatment facilities. The annual prevalence of MG is 72 cases per 1 000 000 population, with an incidence rate of roughly 0.25–2 cases per 1 000 000 people[4]. According to basic health study reports, the incidence of MG in Indonesia is estimated to be 1 case in 100 000[5,6].

Autoantibodies to acetylcholine receptors disrupt neuromuscular transmission, resulting in weakness or decreased strength in skeletal muscles that worsens after activity and improves with rest[7]. Fatigue is caused by a loss in muscle strength and endurance when performing repetitive movements. Fatigue is a subjective and non-specific syndrome characterised by diminished performance as a result of extended cognitive and physical exertion. Previous studies have found that total fatigue scores in MG patients is higher than normal individuals of the same age

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and sex. Fatigue occurs in 75–89% of MG patients, where about 8.2% of patients rated fatigue as a common symptom of MG disease[8,9].

There are 2 types of fatigue, namely peripheral and central fatigue. Peripheral fatigue is muscles fatigue caused by muscles or neuromuscular junctions disorders, whereas central fatigue is a lack of energy and fatigue that is not caused by muscle weakness or discomfort and interferes with physical and mental activity. Fatigue in chronic neuromuscular disease can cause the central nervous system to reduce physical activity via the central activation failure mechanism. Central fatigue is also caused by inflammatory disease at the neuromuscular junction, autonomic dysregulation, and neuroendocrine dysregulation[10]. MG is a disease that causes both peripheral fatigue and central fatigue. This has an influence on physical activity and frequently necessitates adjustments to daily routines, resulting in a loss in quality of life[11].

Walking ability is a key aspect that influences a person's degree of health[12]. MG patients have reduced levels of physical activity when compared to healthy persons. MG patients were observed to spend 78% of their time on sedentary activities, with an average walking pace of roughly 1.1 m/s[3]. physical activity restriction, especially walking, predicts the intensity of fatigue. Reduced physical activity is linked to increased fatigue[10]. fatigue causes a gradual deterioration in walking performance in MG patients. The average distance covered in 60s is significantly reduced in MG patients[9].

Many studies have been conducted on the effects of fatigue on daily activities. A systematic review explained that fatigue causes a decrease in daily physical activity, but the walking capacity in MG patients remains unknown, particularly in Indonesia[10]. This study was aimed to analyse the correlation between fatigue and walking ability in MG patients.

Methods

Participant

Participants in this study were patients with MG class I or II who had eyelid droop (ptosis) after physical activity that improved with rest but was not accompanied by weakness in other muscles[13,14]. Patients with confirmed MG class I and II according to the Myasthenia Gravis Foundation of America (MGFA), aged 18–59 years, cooperative, and normal cognitive function were eligible to participate. Exclusion criteria participants were myasthenic crisis, cardiorespiratory disorders (ischaemic heart disease, resting heart rate greater than or equal to120, hypertension stage II [systolic > 160 mmHg] based on Joint National Committee VII [JNC VII][15], arrhythmia, New York Heart Association (NYHA) grade 2,3,4 heart failure[16], restrictive or obstructive airway disease), have the systemic disease (kidney disease, hepatic serosis), pregnant, balance disorders, visual impairment, recent stroke, erythema, wounds, ulcers, or gangrene on one or both legs, and neuromusculoskeletal and vascular disease in the lower extremities compromising ambulation. Participants are provided with an explanation before the research takes place, and if they agree, they must fill out a consent form without any kind of coercion.

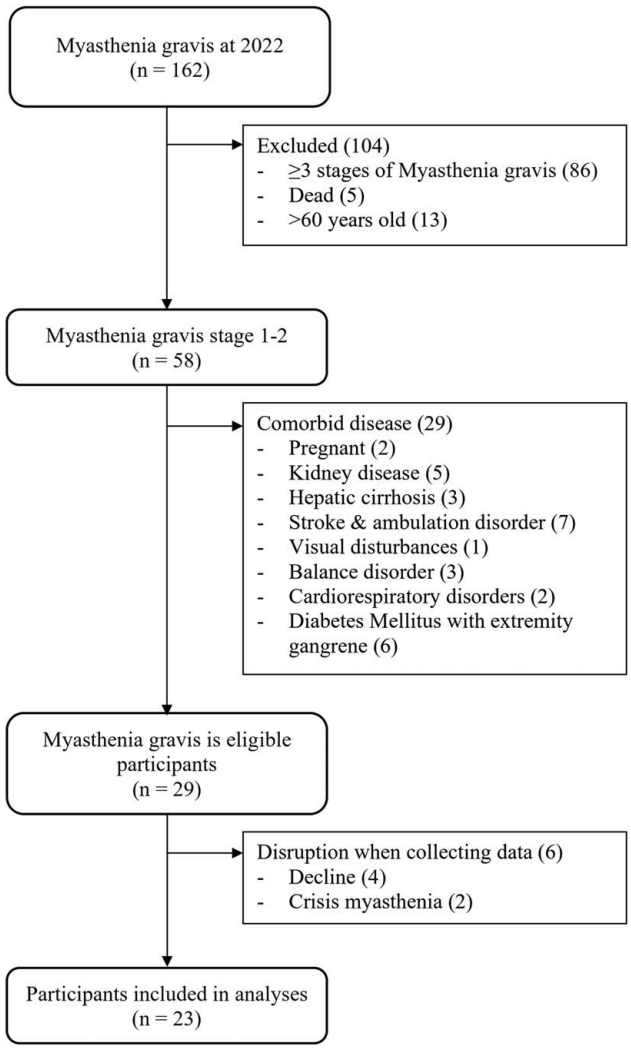

Figure 1. The collecting data process on myasthenia gravis disease was to be participants in this study.

Study design

This study used a cross-sectional design with consecutive sampling. Participants in this study were MG patients with a total of 23 participants (Fig. 1). Data collection was carried out at tertiary hospital in Indonesia from July 2022 to July 2023. This study collected data on fatigue and walking ability. The fatigue severity scale (FSS) was used to assess fatigue, while the 10-metre walking test (10MWT) was used to assess walking capacity. The researchers obtained ethical approval from ethical committee before beginning the study. This study reported the data based on strengthening the reporting of cohort studies in surgery (STROCSS) 2021 guidelines[17].

10-metre walking test procedure

The 10-metre walking test (10MWT) is a walking speed test that is performed over a total distance of 10 metres and consists of 2-metre acceleration, 6-metre of walking monitored by a stopwatch, and 2-metres of deceleration. after the individual was in a standing position with both feet behind the starting line, the test

began with a verbal cue. Each participant was asked to walk to the finish line at their typical everyday pace and at their maximum speed. To remove the effects of acceleration and deceleration, measurements were taken exclusively along the 6-metre track. Time measurement begins when the leading toe crosses the 2-metre mark and ended until the leading toe reached the 8-metre mark[18]. Participants repeated each test two times with a 1-min pause, and the average of the two tests was calculated[19,20]. comfortable walking speed (CWS), maximal walking speed (MWS), and natural cadence were used to assess walking ability[21].

Fatigue severity scale

The FSS is a self-reported fatigue questionnaire that is commonly used in populations with neurological illnesses (systemic lupus erythematosus, multiple sclerosis, amyotrophic lateral sclerosis, fibromyalgia, cancer, and so on) as well as healthy populations. In addition, the FSS can be used to examine specific characteristics of fatigue in MG[11]. The FSS questionnaire consists of 9 questions that assess a person's level of fatigue. Assessment is carried out to assess the effect of fatigue on motivation, activity, physical function, tasks, and interference with work, family, or social life. A Likert scale on a rating of 1 (strongly disagree) to 7 (strongly agree) was utilised. The higher the score, the more severe the fatigue. An average score of less than 4 shows no exhaustion, while an average score of greater than or equal to 4 suggests fatigue. The FSS Indonesian version was declared valid ($r = 0.349$) and reliable ($\alpha = 0.880$)[22].

Statistical analysis

All data obtained in this study were analysed using SPSS statistics 26.0 (IBM Corp., Armonk). The demographic profile was presented as mean, SD, median, interquartile range, minimum (min), maximum (max), and percentage. To begin analysing data distribution, a normality test using the Shapiro–Wilk test was performed. The data analysis used the Pearson correlation and Spearman rank test, which was used to determine the correlation between fatigue and walking ability. In addition, the correlation analysis between gender on fatigue and walking ability was measured by independent *t*-test. The results of the analysis are declared significant if the P value <0.05.

Result

Characteristic of participant

Most participants were female (69.6%) and had early-onset myasthenia gravis (86.9%). The mean age of the participants was 47.7 ± 5.68 years old. All study subjects have generalised MG type. The results of participant BMI measurements were obtained from the highest to the lowest as follows: normal (34.8%), obese grade I (26.1%), overweight (17.4%), underweight (13%), and obese grade II (8.7%). Most participants had no comorbidities, while others had hypertension (25.8%), hypercholesterolaemia (8.6%), polio (4.3%), lipoma (4.3%), sinusitis (4.3%), and nephrolithiasis (4.3%). MG stage based on MGFA including MGFA 1 (39.13%), MGFA 2A (34.78%), and MGFA 2B (26.09%; Table 1).

Table 1

Demographic profile

Variable	*n* (%)
Sex	
Male	7 (30.4)
Female	16 (69.6)
Onset age	
0–49 years old (EOMG)	20 (86.9)
≥ 50 years old (LOMG)	3 (13.1)
Type MG	
General	23 (100)
Ocular	0
BMI	
Underweight	3 (13)
Normal	8 (34.8)
Overweight	4 (17.4)
Obese grade I	6 (26.1)
Obese grade II	2 (8.7)
Comorbid disease	
Hypertension	6 (26.1)
Hypercholesterolaemia	2 (8.7)
Polio	1 (4.3)
Lipoma	1 (4.3)
Sinusitis	1 (4.3)
Nephrolithiasis	1 (4.3)
MGFA	
MGFA 1	9 (39.13)
MGFA 2A	8 (34.78)
MGFA 2B	6 (26.09)

EOMG, early-onset myasthenia gravis; LOMG, late-onset myasthenia gravis; MG, myasthenia gravis; MGFA, myasthenia gravis foundation of America.

Fatigue score

The mean fatigue value for the participants was 5.46 ± 1.13, with a median of 5.67 (5.00 – 6.28). Fatigue means values based on MGFA, including MGFA 1 of 5.32 ± 1.15, MGFA 2A of 5.5 ± 1.11, and MGFA 2B of 5.61 ± 1.30 (Table 2). The median fatigue level value at MGFA 1 was 5.44 (5.33–5.78), with a min of 2.44 and a max of 6.56. The median fatigue value at MGFA 2A is 5.78 (4.94–6.24), with a min-max of 3.67–6.89. Meanwhile, in MGFA 2B, the median fatigue value was 5.55 (4.78–6.75), with a min of 3.89 and a max of 7.

Walking ability

CWS measurements obtained a mean of 1.10 ± 0.11 m/s with a median of 1.14 (1.03–1.16) m/s. CWS values at each MGFA level include 1.05 ± 0.14 m/s with a median of 1.08 (0.8–1.23) m/s (MGFA 1), 1.11 ± 0.07 m/s with a median of 1.12 (0.99–1.21) m/s (MGFA 2A), and 1.16 ± 0.10 m/s with a median of 1.17

Table 2

Results of fatigue levels and walking ability measurements in MG patients

Myasthenia gravis	Fatigue	CWS	MWS	Natural cadence
MGFA 1	5.32 ± 1.15	1.05 ± 0.14	1.26 ± 0.16	107.56 ± 9.07
MGFA 2A	5.5 ± 1.11	1.11 ± 0.07	1.31 ± 0.16	110.00 ± 6.07
MGFA 2B	5.61 ± 1.30	1.16 ± 0.10	1.40 ± 0.09	117.17 ± 3.43

CWS, comfortable walking speed, MG, myasthenia gravis; MGFA, myasthenia gravis foundation of America; MWS, maximal walking speed.

Table 3

Correlation of fatigue levels on walking ability in the MG patients.

	CWS		MWS		Natural Cadence	
Fatigue severity	***r***	***P***	***r***	***P***	***r***	***P***
MG total	− 0.141	0.520	− 0.169	0.442	− 0.050	0.822
MGFA 1	− 0.628	0.070	− 0.653	0.057	0.067	0.864
MGFA 2A	− 0.083	0.845	− 0.322	0.437	− 0.417	0.304
MGFA 2B	0.154	0.771	− 0.355	0.490	− 0.436	0.388

CWS, comfortable walking speed; MG, myasthenia gravis; MGFA, myasthenia gravis foundation of America; MWS, maximal walking speed.

(1.00–1.28) m/s (MGFA 2B). Meanwhile, the average participant MWS value was 1.31 ± 0.15 m/s with a median of 1.28 (1.20–1.46) m/s. The results of the MWS measurements for each MGFA obtained different values (Table 2). In MGFA 1, the average MWS value was 1.26 ± 0.16 m/s with a median of 1.21 (1.10–1.58) m/s. MGFA 2A's average MWS value was 1.31 ± 0.16 m/s with a median of 1.24 (1.10–1.52) m/s. Meanwhile, in MGFA 2B, the average MWS value was 1.40 ± 0.09 m/s with a median of 1.40 (1.25–1.50) m/s.

Participants' natural cadence value was 110.91 ± 7.74 steps/min with a median of 110 (106–117) steps/min. The mean natural cadence value in MGFA 1 was 107.56 ± 9.07 steps/min, in MGFA 2A, it was 110 ± 6.07 steps/min, and in MGFA 2B, it was 117.17 ± 3.43 steps/min (Table 2). Meanwhile, the median value of natural cadence in MGFA 1 was 107 (104–110) steps/min. In MGFA 2A, it was 110 (107–111.5) steps/min; in MGFA 2B, it was 117.5 (115.25–119.75) steps/min.

Correlation of fatigue on walking ability in MG patients

There is no significant correlation between fatigue and walking ability in MG patients, including FSS vs. CWS ($r = -0.141$; $P = 0.520$), FSS vs. MWS ($r = -0.169$; $P = 0.442$), and FSS vs natural cadence ($r = -0.050$; $P = 0.822$). The results of the analysis of FSS vs. CWS for each MGFA did not obtain a significant correlation, which at MGFA 1 obtained $r = -0.628$ and $P = 0.070$, MGFA 2A obtained $r = -0.083$ and $P = 0.845$, and MGFA 2B obtained $r = 0.154$ and $P = 0.771$. In the FSS vs. MWS analysis, the following results were obtained: MGFA 1 ($r = -0.653$; $P = 0.057$), MGFA 2A ($r = -0.322$; $P = 0.437$), and MGFA 2B ($r = -0.355$; $P = 0.490$). Whereas in FSS vs. natural cadence for each MGFA, no significant correlation was found, including MGFA 1 ($r = 0.067$; $P = 0.864$), MGFA 2A ($r = -0.417$; $P = 0.304$), and MGFA 2B ($r = -0.436$; $P = 0.388$; Table 3).

There is no significant comparison FSS value between male and female in MG patients ($t = -1.455$; 95% CI = − 1.766 to 0.311; $P = 0.160$). In walking ability, there were also no significant comparison on gender domains including CWS ($t = 0.231$; 95% CI = − 0.094 to 0.118; $P = 0.819$), MWS ($t = -0.606$; 95% CI = − 0.186 to 0.102; $P = 0.551$), and natural cadence ($t = -1.019$; 95% CI = − 10.858 to 3.715; $P = 0.320$).

Discussion

Fatigue is a common complaint in neuromuscular disease and significantly impacts the patient's quality of life. In MG patients, the disturbance of neuromuscular transmission causes fluctuating muscle weakness and triggers fatigue. Even though complaints of muscle weakness in MG patients have stabilized with routine treatment, complaints of fatigue are still felt and burden patients[23].

Fatigue in MG can result from central and peripheral fatigue[24]. There are various instruments for assessing fatigue, but they have yet to become a standard. This study used the FSS questionnaire to measure the degree of fatigue felt by MG patients. Assessment with the FSS was carried out to see the effects of fatigue on motivation, physical activity, and function, carrying out tasks, disruption to work, family, and social life. Interpretation of the results indicates that the higher the FSS score, the more severe the perceived degree of fatigue. An average score of less than 4 indicates no fatigue, while an average score of greater than or equal to 4 indicates fatigue[22]. The average FSS increases with increasing severity. A previous study stated that approximately 80% of MG patients complained of fatigue, and more than 50% experienced physical and cognitive fatigue[23]. MG patients have a high prevalence of fatigue, which can negatively impact daily activities and quality of life. Another study also found that the severity and depressive status were independent risk factors associated with the degree of MG fatigue[8].

The walking ability of MG patients in this study was measured using comfortable walking speed, maximum walking speed and cadence. The normal value for healthy individuals without ambulation disorders is 100 steps/min to participate in the community and moderate-intensity aerobic activity[25]. The walking ability data in this study are by previous studies that assessed the physical activity patterns of MG patients, in which most MG patients spend their time doing sedentary activities, with an average walking speed of around 1.1 m/s, which is below the normal population walking speed value[3]. The decline in walking performance was gradual in MG patients, and the average distance covered in the 60s decreased significantly in MG patients[9]. Another study stated that the average value of walking speed in MG patients reached 1.54 and 1.51 m/s[26].

This study explains the evidence that fatigue does not have a significant association with walking ability but has a substantial connection with individual walking capacity[27]. Previous studies also supported this result, which stated that fatigue has no significant association with walking ability. Several statements say that subjective fatigue affects walking ability, but objective fatigue impacts individual weakness, meaning it impacts the quality of walking capability, not ability[28]. Previous studies assessed the relationship between fatigue and walking endurance in MG patients using the 6-minute walking test, which found a decrease in walking speed between the first and sixth min[26]. Other studies have shown that central and peripheral fatigue do not affect the speed of muscle contraction during submaximal force. Fatigue generally affects when doing maximum contractions. This is relevant where walking, running or other daily activities require the production of submaximal contractions faster than maximal contractions[29].

There was no significant difference in walking speed between stroke patients with and without fatigue. Fatigue is unrelated to fitness variables or ambulation activity levels, but fatigue causes decreased motivation and triggers depression, which can cause decreased physical function[30]. Multiple sclerosis patients also showed no association between peripheral fatigue and perceived fatigue on walking performance. The study found other factors,

such as muscle weakness and spasticity, which are the main determinants of gait disturbances. Nonetheless, increased fatigue is still associated with increased disability[31].

In our study, gender did not affect fatigue and walking ability. However, in terms of prevalence, it has been proven that the number of females is greater than that of males in MG incidence. The appearance of MG symptoms is detected earlier in female than in male[32]. In addition, the severity of MG is more common in female than male, which correlates with a higher female prevalence[33]. This condition is caused by preferential inactivation of the X chromosome inherited from parents, which is associated with the prevalence of several autoimmune diseases in female, one of which is MG disease[34]. According to previous research, the prevalence of MG patients is more female, but we cannot prove that gender affects fatigue level and walking ability in MG patients. This study's strengths include proving there is no association between fatigue and walking ability. Fatigue affects an individual's walking quality such as speed, capability, and endurance. Meanwhile, the study's limitations include the number of participants needing to be more significant because the participants collecting are limited and willing to participate in the study. So, in the future, the participant size is expected to be even more significant for further research. In future studies, it is necessary to consider assessments of sedentary life and mental status in MG patients.

Conclusion

There is no significant correlation between fatigue and walking ability, including CWS, MWS, and natural cadence. There is no significant correlation between fatigue and walking ability not only at MGFA 1 but also at MGFA 2A and 2B.

Ethical approval

We have conducted an ethical approval based on the Declaration of Helsinki with a registration study at the Health Research Ethics Committee Universitas Airlangga School Medicine, Surabaya, Indonesia.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

L.K.: data curation, formal analysis, project administration, resources, writing—original draft; I.S.: conceptualization, investigation, methodology, supervision, writing—review and editing; I.P.A.P.: data curation, investigation, methodology, validation; M.A.: investigation, software, supervision, validation; P.S.: resources, supervision, visualisation.

Conflicts of interest disclosure

All authors declare no conflict of interest.

Research registration unique identifying number (UIN)

Registry used: Health Research Ethics Committee, Universitas Airlangga School Medicine, Surabaya, Indonesia. Unique identifying number or registration ID: 0927/EC/KEPK/FKUA/2022. Hyperlink to your specific registration (must be publicly accessible and will be checked): -.

Guarantor

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Data availability

Data are available upon reasonable request.

Provenance and peer review

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