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Association between Fatigue Level with Disease Severity in Myasthenia Gravis Patients

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Abstract

Background: Fatigue is a common symptom and has a greater effect on daily living of myasthenia gravis (MG) patients than has muscle weakness. Latest evidence suggested that fatigue in MG negatively impact disease severity. The relationship between fatigue level with disease severity has never been explored in MG patients. **Aims.** The study aimed to determine the association between fatigue level and disease severity in myasthenia gravis patients at Dr. Soetomo Public Hospital Surabaya. **Method.** A cross-sectional was used in this research. Participants of the research were patients with myasthenia gravis in Neurology Clinic, Dr. Soetomo Public Hospital Surabaya. The period of data collection was from April to June 2021. Fatigue level measured with Fatigue Severity Scale (FSS) questionaire and disease severity measured with Myasthenia Gravis Composite (MGC) score. Data analysed using SPSS version 22.0 with significances of $p < 0.05$. **Results**. There were 37 participants consisted of 14 males and 23 females. Mean age of participants 45,03 ± 11,69. Mean age of onset was 40,38 ± 12,60. The mean FSS was 4,02 ± 1,93 and mean MGC was 5,24 ± 5,64. From all participants, we found that about 24 patients (64,9%) showed severe fatigue and 22 patients (58,5%) have severe disease status. The Chi-Square correlation test analysis indicates a significant association between FSS mean score and MGC mean score (p = 0.009, OR at 6,750) 95% CI (1,51-30,16). **Conclusion**. There was an association between fatigue level and disease severity in myasthenia gravis patients.

Keywords: *Fatigue Level; FSS; Diasease Severity; MGC; Myasthenia Gravis.*

Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by IgG autoantibodies that attack the acetylcholine, MuSK, or LRP4 receptors on neuromuscular junction (NMJ) postsynaptic membrane with typical symptoms of fatigue and fluctuated skeletal muscle weakness that worsens with activity and improves after rest. The incidence of MG is estimated to be 8-10 cases per 1,000,000 population per year with a prevalence of 150 - 250 per 1,000,000 population[1]. Based on the 2010 Basic Health Research report, the incidence of MG in Indonesia it is estimated that 1 case out of 100,000 people[2]. Symptoms of MG are very varies with initial symptoms of ptosis and/or diplopia in 85% of patients and progresses to generalized MG within 2 years of onset in 80% of cases[3]. Respiratory muscles can be affected in up to 20% of cases of acetylcholine receptor-associated MG (AChR MG) causing a myasthenic crisis and requiring assistance ventilator[4]. MG-related health economic costs in 8 countries spanning 4 continents (Europe, North America, South America and Asia)

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shows that per year direct medical costs estimated at 760 - 28,780 USD, home care costs between 2,550 - 164,730 USD and indirect costs estimated at 80 - 3,550 USD[5].

Current growing evidence suggests fatigue is a symptom which is common and has a greater effect than muscle weakness in MG patients in daily life. Even MG patients who have been in permanent remission experiencing symptoms of fatigue[6]. Fatigue is a symptom that is getting interesting to study on neuromuscular disorders and their several studies of fatigue in MG indicate an increased awareness of the importance of these symptoms. Fatigue is a subjective symptom of physical fatigue and/or mental, extreme and persistent weakness or depletion of energy[7]. Fatigue can be classified as peripheral fatigue with disturbances in the components of the motor unit and central fatigue originating from disorders of the central nervous system. Another type of fatigue is physical fatigue and mental fatigue which central fatigue contains both types of fatigue as the main features[8]. In this study, researchers followed the latest taxonomy related to the use of the term fatigue which refers to the subjective sensation of tiredness and fatigability show objective changes in muscle and cognitive performance[9].

Fatigue is a complex, non-specific and subjective symptom making it difficult to evaluate and measure. Fatigue in MG is peripheral fatigue, however studies show that MG patients also experience cognitive and mental fatigue and significantly more than healthy individuals as controls. Prevalence fatigue in myasthenia gravis is estimated to be between 75% to 89%[9]. Assessment of fatigue usually relies on patient self-report questionnaires. Questionnaire Fatigue Severity Scale (FSS) can be used to measure the degree of fatigue, both in the normal population and in those with severe neurologic disorder in various health facilities. Assessment is carried out to see the relationship of fatigue to motivation, activity, physical function, carrying out tasks, distractions to work, family and social life[10,11].

MG is a chronic disease and lasts for a long time so that health services focus on hindering progression, management of symptoms and severity of disease and improve the quality of MG patient life[12]. Assessment of the severity of disease in MG patients is very important because it is the main parameter of disease management outcomes MG[13]. Measurement of the severity of the disease can be done using Myasthenia Gravis Composite (MGC) score recommended by MGFA for use in MG research. The MGC scale has advantages of being simpler and combining patient history and examination by a clinician[14].

Growing evidence reports that fatigue has a negative impact on disease severity[15]. However, the literature on fatigue in MG is still lacking rare and the relationship between the level of fatigue with the severity of the disease MG patients is not known. Therefore, the researchers tried to conduct a study to determine the relationship between the level of fatigue measured using FSS with the degree of disease severity as measured by MGC in MG patients.

Materials and Methods

This study was an analytical observational study with a cross-sectional approach myasthenia gravis patients, who were in the neurology clinic Dr. Soetomo Public Hospital Surabaya. The data collected covers a period of 3 months from April to June 2021. The primary data used in this study include: (1). age, (2). gender, (3). age at onset, (4). Fatigue Severity Scale (FSS) and (5) Myasthenia Gravis Composite (MGC) Score The inclusion criteria in this study were patients with myasthenia gravis who have visited Neurology Clinic Dr. Soetomo Hospital with current age over 18 years.

The fatigue level of the studied myasthenia gravis patients was assessed using Fatigue Severity Scale (FSS). The FSS assessment is divided into: (a) mean score <4: mild fatigue and (b) Mean score ≥ 4: severe fatigue. The MGC score is divided into: (a) score <4: mild status severity and (b) score ≥ 4: severe status severity. Age at onset was classified into early onset < 50 years and late-onset ≥ 50 years.

The collected data was analyzed using the Statistical Package for the Social Sciences (SPSS) v22 for Windows (IBM Inc., Chicago, IL). Chi-square test with the calculation of odds ratio (OR) and 95% confidence interval was used to determine association with considered statistically significant when the value was $p<0.05$.

Results

The total number of research subjects analyzed were 37 subjects. Demographic characteristics based on age, the youngest age of the subject was 20 years old and the oldest 68 years old, with a mean age of the study subjects 45.03 ± 11.69 years. Based on the age of onset MG symptoms, the age of onset the earliest age is 16 years, while the last onset age is 66 year. Based on gender, male 14 subjects (37.8%), while female 23 subjects (62.2%). Furthermore, the research subjects obtained with severe FSS 24 subjects (64.9%) and mild FSS 13 subjects (35.1%). The average value of the FSS is 4.02 ± 1.93. A total of 22 (58.5%) subjects had moderate-severe MGC and 15 (41.5%) subjects had mild MGC. Score the average total MGC was 5.24 ± 5.64. (table 1).

Table 1. Demography data of participants

	Total (%)	Mean	Std. Deviation
Age <50 yrs ≥50 yrs	 23 (62,2) 14 (37,8)	45,03	11,69
Gender Male Female	 14 (37,8) 23 (62,2)		
Age at onset <50 yrs ≥50 yrs	 28 (75,7) 9 (24,3)	40,38	12,60
Fatigue Level FSS <4 FSS ≥4	 13 (35,1) 24 (64,9)	4,02	1,93
Disease severity MGC <4 MGC ≥4	 15 (41,5) 22 (58,5)	5,24	5,64

Table 2 shows that there were 18 subjects (75%) with Severe FSS with moderate to severe disease and 6 subjects with Severe FSS (25%) had mild disease severity, whereas 4 subjects (30,8%) with mild FSS had moderate to severe disease severity and 9 subjects (69,2%) with mild FSS had mild disease severity. There was a significant relationship between the level of fatigue (FSS) and the degree of disease severity (MGC) and statistically significant with p value = 0.009 and OR = 6.75 (95% CI 1.51-30.16) which means the level of fatigue (FSS) is increasing 6.75 times the risk of experiencing moderate to severe disease severity.

Table 2. The chi-square analysis test between FSS and MGC

Fatigue Level (FSS)	Disease Severity (MGC)		p value	95% Confidence Interval
	Moderate-Severe	Mild		
FSS ≥ 4	18	6	0.009	(OR 6,750) 95% CI (1,51-30,16)
FSS < 4	4	9		
Total	22	15		

Discussion

This research is an analytic observational study with cross sectional design to determine the relationship between the level of fatigue with the severity of MG disease. Sampling has done with consecutive sampling from April to June 2021 at the Neurology Clinic. The sample size is determined by the formula sample size for unpaired categorical analytic research, the value of proportion effect in case group (p1) and control group (p2) was determined based on previous research and obtained a minimum sample size 32 people. The sample size obtained in this study was 37 samples. Statistical analysis using IBM SPSS software version 22.0. Research data analyzed by Chi Square test. This research has limitations because did not analyze the MG type variable based on the type of antibody found as confounding variable due to no routine examination of antibody levels in myasthenia gravis patients.

The demographic data of the research subjects included age and gender. Then, analyzing relationship between age and sex with the severity of MG disease. Characteristics based on demographic data obtained the youngest age of the subject study was 20 years old and the oldest was 66 years with a mean age of 45 ± 11,694. There was no significant relationship between the patient's age and the severity of the disease. Subjects with male 14 subjects (37.8%), while women were 23 subjects (62.2%) with a ratio of female : male = 3:2, which is based on statistical analysis also not found a significant relationship between gender and the degree of disease severity. The results of this study are in accordance with the study by Fan et al. at 985 MG patients, the mean age of the study subjects was 40.8 years with a ratio of 3:1 women are more affected than men. This demographic data is similar with the study by Zhang et al. which mentions the ratio of women: men of 3:1 at the age of < 40 years, then balanced at the age of 40-50 years and more about men aged > 50 years. Sex hormones play a role in predisposition to MG and involvement of the hormone estrogen causes thymic hyperplasia thereby increasing the risk of developing MG, especially early-onset MG[16].

Citarak, et al. in his research stated that age and gender has no effect on the clinical degree of disease and the total value of the patient's muscle strength myasthenia gravis. When age and sex are related to clinical grade disease, there was no difference in the clinical severity score between women and men and the age of patients who are less than 50 years more than equal to 50 years. Only mentioned in the study that muscle weakness is more severe in men 50 years of age compared to younger men and women 50 years of age. This research according to research by Citarak et al. above which is likely caused by the relatively homogeneous age of the subjects of this study, i.e. most of the are in the young adult range (<50 years)[17].

In this study the authors linked the age of onset of MG symptoms with the severity of MG disease. Obtained research subjects with age the earliest onset of MG symptoms was 16 years, while the age of symptom onset was late at age 66 years with a mean age

of symptom onset of study subjects 40.4 ± 12.6 years. Bivariate data analysis showed that age of symptom onset as confounding variables did not find a significant relationship to the degree of MG disease severity. The relationship between the level of fatigue (FSS) with the degree MG disease severity was analyzed in this study. Subject research with severe FSS 24 subjects (64.9%) and mild FSS 13 subjects (35.1%), which based on bivariate analysis showed that the level of fatigue (FSS) has a significant relationship with the severity disease (MGC) both clinically and statistically. The results of this study are not in accordance with the study conducted by Zivkovic et al. who concluded that late-onset patients were associated with the presence of thymoma and are more severe and more difficult to treat. Thymoma is often associated with an autoimmune process. Neoplastic epithelial cells in thymoma expresses several antigen-like antibodies that attack acetylcholine receptors, the muscle protein titin and ryanodine that cause more severe MG[18]. The study by Ruiter et al. reported that the fatigue scores are associated with more severe disease severity measured by MGC, QMG, MGII and MG-ADL. Muscle fatigability related to the pathogenesis of MG and the patient's perception of fatigue play a role in increasing the severity of the disease[3].

Conclusions

Analysis of the chi-square test showed that the variable affecting diasease severity in patients myasthenia gravis was the fatigue level. Patients with severe fatigue were 6,75 times more likely to experience severe disease status than patients with mild fatigue. Therefore, patients and clinicians should be more careful in managing fatigue in mysthenia gravis patients.

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