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ORIGINAL ARTICLE

Physical and mental fatigue in myasthenia gravis and its correlation with other symptoms

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Abstract

Introduction Muscle weakness and easy fatigability are the clinical hallmarks of myasthenia gravis (MG). However, fatigue perception, which can be seen quite often in myasthenic patients, and its effect on the quality of life, irrespective of motor deficit, has not been elucidated yet. The aim is to evaluate the frequency of fatigue in myasthenic patients with nearly full muscle strength and the effect of fatigue on quality of life by assessing its correlation with other symptoms.

Methods Fifty-three patients with ocular or mild generalized MG in remission or minimal manifestations completed the questionnaires measuring the severity of MG and quality of life (MG Composite Scale and MG-Activities of Daily Living Profile). Both patient group and control group (53 healthy volunteers)completed the scales assessing fatigue [Fatigue Assessment Scale (FAS) and Fatigue Impact Scale (FIS)], depression [Beck Depression Inventory (BDI)] and sleep (Epworth Sleepiness Scale). Disease severity was assessed using MG Foundation of America (MGFA) and MGFA Post-Intervention Status classifications.

Results FAS, FIS physical and BDI scores were significantly higher in patients compared to the control group ($p=0.003$, $p=0.001$, and $p=0.003$, respectively) and fatigue was associated with depression and daytime sleepiness. Inpatient group, depressive symptoms and daytime sleepiness were higher in females ($p=0.019$ and $p=0.013$). The mean values of FIS total and cognitive scores were higher in patients with generalized MG ($p=0.033$ and $p=0.045$). Fatigue scores correlated with motor signs.

Discussion Fatigue can be seen in MG independently from muscle weakness and is an important symptom worsening the quality of life.

Keywords Myasthenia gravis · Fatigue · Quality of life · Depression · Sleepiness

Abbreviations

BDI	Beck depression ınventory
BMI	Body mass index
EMG	Electromyography
ESS	Epworth sleepiness scale
FAS	Fatigue assessment scale
FIS	Fatigue ımpact scale
fT4	Free thyroxine
IBM SPSS-20	Statistical package for social sciences, Chicago, Illinois, USA
MG	Myasthenia gravis
MG-ADL	Myasthenia gravis activities of daily living profile
MGC	Myasthenia gravis composite scale
MGFA	Myasthenia gravis foundation of America
MGFA-PIS	Myasthenia gravis foundation of America post-ıntervention status
MGQoL-15	Myasthenia gravis quality of life-15
MM	Minimal manifestations
TSH	Thyroid stimulating hormone

Introduction

Autoimmune myasthenia gravis (MG) is the most common acquired neuromuscular junction disorder. Antibodies against the components of post-synaptic muscle membrane cause the disease. Painless, fluctuating and reversible muscle weakness and worsened with exercise is the most important

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symptom of MG. The disease is not expected to shorten the lifespan significantly but has been shown to adversely affect the quality of life [1, 2].

Muscular (physical) fatigue typically develops or worsens with physical activity in MG, clinical follow-up and treatment strategies focus on this muscle fatigability symptom. However, in recent years, it has emerged that feeling of physical and mental (cognitive) fatigue other than muscle fatigability can be seen in MG like in other neurological or autoimmune systemic diseases [3–5]. Fatigue is used to describe a subjective feeling of exhaustion, while fatigability is used as an objective term to indicate a decline in performance [5]. In neurologic practice, it is difficult to distinguish between 'fatigability' and 'feeling fatigue' in MG patients, because patients with reduced muscle strength often have both [4, 5]. There is also an opinion that the presence of fatigue in ocular MG patients represents a subclinical generalized MG or a condition before the generalization of the disease [6]. Presence of somnolence, depression or apathy can mimic fatigue and fatigue can be seen primarily in MG but also secondary to many factors such as anemia, physical limitations, respiration or sleeping problems.

The aim of this study is to evaluate the frequency of fatigue symptoms in myasthenic patients in remission or nearly full muscle strength and to reveal the effect of fatigue on quality of life by assessing its correlation with other non-motor symptoms such as depression and sleepiness. Therefore, our purpose is to increase clinical awareness of signs and symptoms other than muscle weakness in MG patients and to guide future studies to improve the quality of life of patients.

Methods

This study was conducted between December 2018 and June 2019 at the outpatient clinic of Neuromuscular Diseases, Marmara University Hospital, Istanbul, Turkey. The Ethics Committee of the Marmara University School of Medicine approved the study protocol (No. 09.2018.572) and written informed consent for study participation was obtained from all participants.

Study population

Consecutive patients with a confirmed diagnosis of ocular or generalised MG, between the ages of 18–70 years, were prospectively recruited from the outpatient clinic of Neuromuscular Diseases during regular medical visits. Diagnosis of MG was based on history, physical examination and at least one positive ancillary test, including electrophysiological study or detection of MG-specific antibodies. Patients in Myasthenia Gravis Foundation of America (MGFA) 1 (ocular disease) or MGFA 2A class [generalised disease but in complete or pharmacological remission or minimal manifestations (MM)] were included in our study. Patients with a history of an illness suspected to cause physical fatigue, pregnant patients, patients with dementia and significant motor weakness at the time of assessment were not included in the study. General muscle involvement is divided into subgroups as mild, moderate and severe by MGFA classification. MGFA-Post-Intervention Status (MGFA-PIS) is designed to evaluate the clinical status of patients at any time after treatment has started [7]. This scale standardizes and evaluates the clinical course and neurological examination findings of MG patients by combining with symptomatic, immunosuppressive and immunomodulating therapies. We also recruited age-gender-matched healthy volunteers without any systemic or neurological disease expected to cause fatigue among colleagues and healthy relatives of our patients with similar demographic and lifestyle features, admitted to our outpatient clinics. People with uncontrolled diabetes, hypertension and hypothyroidism were excluded. The participants in both patient and control groups did not use to perform regular physical exercise.

Patients were evaluated with detailed history and neurological examination. The demographic features of patients, age at onset of myasthenic complaints, duration of the disease, antibody positivity, thymus pathology or thymectomy, if performed, the electromyography (EMG) results and current medication were noted. The demographic characterization of the control group was also noted.

Questionnaires

The patient group completed questionnaires measuring the severity of MG and quality of life [MG Composite Scale (MGC) and MG-Activities of Daily Living Profile (MG-ADL), MG Quality of Life-15 (MGQoL-15)], while both the patient and control groups completed scales assessing fatigue [Fatigue Assessment Scale (FAS) and Fatigue Impact Scale (FIS)], depression [Beck Depression Inventory (BDI)], and sleep [Epworth Sleepiness Scale, (ESS)]. If available, validated Turkish versions of questionnaires were used, as in the case of the MGQoL-15, FIS, BDI and ESS [8–11]. The Turkish-translated versions of MGC, MG-ADL and FAS were used. In addition, the relationship between the patient's fatigue and current medication(steroids, other non-steroid immunosuppressive and symptomatic drugs), body mass index, educational status, gender, presence of concomitant autoimmune thyroid disease were evaluated.

MGC scale consists of 10 test items,4 items from patient history and 6 from the examination, measuring MG symptoms and signs, and higher scores indicate worse prognosis [12]. MG-ADL is a scale with eight questions including ocular, oropharyngeal, respiratory and extremity functions

to evaluate the impact of MG symptoms on daily living, and the total score ranges from 0 to 24 [13]. MGQoL-15 is a disease-specific QoL measure evaluating the symptoms for last month and composed of 15 items. Total scores range from 0 to 60 and higher scores indicate the worse health-related quality of life [14].

FAS is a 10-item self-report scale, 5items about physical and 5items about mental fatigue, and by this scale, both physical and mental fatigue are evaluated together [15]. A score of 10 to 21 indicates no fatigue, and a score of 22–50 indicates fatigue. FIS consists of 40 items and was designed to evaluate the impact of fatigue on cognitive, physical and psychosocial aspects over the last month [16]. The total score ranges from 0 to 40 (physical and cognitive FIS) and 0–80 (psychosocial FIS).

Considering that the presence of depression may negatively affect the quality of life and cause a feeling of fatigue, BDI was applied to both the patient and control groups. It is based on clinical observations, including symptoms seen in depression [17]. Total scores ranges from 0 to 63 and patients, with scores over 10 points were accepted as 'patients with depression'. As increased daytime sleepiness can cause a feeling of fatigue and decrease the quality of life, ESS was applied to both the patient and control groups. It consists of eight questions to determine daytime sleepiness during the last month [18]. Scores above 10 were considered abnormal as they indicated increased daytime sleepiness. Considering that they may affect fatigue, hemoglobin, thyroid-stimulating hormone (TSH), free thyroxine (fT4), and vitamin D levels of the patients were also evaluated.

Statistical analysis

IBM SPSS-20 (Statistical Package for Social Sciences, Chicago, IL, USA) package program was used for statistical analysis. Pearson's Chi-Square test and Fisher Exact test were used to compare qualitative data. Spearman's correlation analysis was applied for the relationship of fatigue scales (FAS, FIS) with MGQoL-15, MG-ADL, MGC, BDI, ESS, age, duration of disease, educational status, and vitamin D levels. In the comparison of quantitative data, Mann–Whitney *U* test and Kruskal–Wallis test were used in the case of two or more than two groups, respectively. The results were evaluated at 95% confidence interval and $p < 0.05$ significance level.

Results

A total of 53 patients (31 females and 22 males) and 53 age-gender matched healthy controls were included in the study. The mean age of the patient and control groups were 48.0 ± 13.3 and 47.6 ± 13.3, respectively. There was no statistically significant difference between the two groups in terms of age, body mass index (BMI) and educational status ($p = 0.726$, $p = 0.108$ and $p = 0.286$, respectively). In patient group, 8 patients had hypothyroidism, 2 patients had hypothyroidism and hypertension, 1 patient had diabetes mellitus, and 5 patients had hypertension. In the control group, 8 controls had hypertension, 5 controls had hypothyroidism and 2 controls had diabetes mellitus. All of these comorbidities (patient and control groups) were under control with medical treatment and all the participants were euthyroid when they were included in the study. The median value of MGC scores of the patients was 2 (interquartile range: 0–4). The detailed demographic and clinical data of the patient and control groups are given in Tables 1 and 2.

When patient and control groups were compared in terms of fatigue, depression and sleepiness, the patient group had higher scores in all scales. In patient group, the mean values of FAS, FIS physical and BDI were significantly higher than control group ($p = 0.003$, $p = 0.001$ and $p = 0.003$, respectively). FIS total, FIS cognitive, FIS social, and ESS average scores indicated no significant difference between the two groups ($p = 0.329$, $p = 0.383$, $p = 0.543$, and $p = 0.519$, respectively). When the patients were evaluated according to gender, we found no significant difference in fatigue scales (FAS and FIS) between female and male patients whereas BDI and ESS scores were significantly higher in females compared to males ($p = 0.019$ and $p = 0.013$, respectively). The comparison of the patient and control group in terms of fatigue, depression and sleepiness and each group within themselves according to gender is given in Table 2.

Twenty-three (43%) of the patients were ocular MG, and thirty (57%) of the patients were generalized MG. In the subgroup analyses, when ocular MG patients were compared with the control group in terms of fatigue, depression and sleepiness, only the mean BDI was found to be significantly higher in the patient group ($p = 0.018$), and no significant difference was found in FAS, FIS and ESS. The mean values of FIS total and FIS cognitive were found to be significantly higher in generalized MG compared to ocular MG ($p = 0.033$ and $p = 0.045$), and no significant difference was found between the two groups in terms of FIS physical, FIS social, FAS, depression and sleepiness scales. When the patients were divided into subgroups according to the antibody seropositivity, disease onset time (early or late), thymectomy and treatment status (immunosuppressive, pyridostigmine or steroid), there was no significant difference in terms of FAS, FIS, BDI and ESS scales. Detailed analysis is given in Table 3.

The association of fatigue scales with disease severity, quality of life, depression and sleepiness scales in MG patients were evaluated with Spearman's correlation analysis. FIS total, FIS physical, and FIS social were found to have a significant positive correlation with MG-QoL15

Table 1 Clinical characteristics of the patient group

	n = 53		*n* = 53
Age at diagnosis*	43.2 ± 14.3	**Thymectomy****	12 (22%)
Duration of disease (months)*	61.0 ± 59.3	**Thymus pathology****	
Disease subtype		Thymic hyperplasia	2 (4%)
Early onset	32 (60%)	Thymoma	8 (15%)
Late onset	21 (40%)	**Thyroid comorbidity****	10 (19%)
Ocular MG**	23 (43%)	**Treatment****	
MGFA-PIS**		Pyridostigmine	33 (62%)
CSR	11 (21%)	Steroid	11 (21%)
PR	6 (11%)	Azathioprine	7 (13%)
MM-1	3 (6%)	Rituximab	1 (2%)
MM-2	4 (7%)	Steroid + azathioprine	7 (13%)
MM-3	16 (30%)	Mycophenolate mofetil + steroid	1 (2%)
MGFA 1	13 (25%)	Rituximab + steroid	2 (4%)
Antibody**		Immunoglobulin + steroid	1 (2%)
Anti-AChR (+)	24 (45%)	Immunoglobulin + azathioprine	1 (2%)
Anti-MuSK (+)	5 (9%)	**Biochemical tests ***	
Seronegative	22 (41%)	Vitamin D (g/L)	20.22 ± 10.44
Electrophysiology**		TSH (mU/L)	1.67 ± 1.17
RNS decrement	14 (26%)	fT4 (ng/dL)	0.84 ± 0.14
Anormal jitter	33 (62%)	Hemoglobin (g/dL)	13.03 ± 1.48

Anti-AChR acetylcholine receptor antibody; *Anti-MuSK* muscle specific kinase antibody; *RNS* repetitive nerve stimulation; *CSR* complete stabil remision; *MG* myasthenia gravis; *MGFA* myasthenia gravis foundation of America; *MGFA-PIS* MGFA post-ıntervention status; *MM* minimal manifestations; *PR* pharmacological remission; *sT4* free thyroxine; *TSH* thyroid-stimulating hormone

*Arithmetic mean ± standard deviation, **n (%)

Table 2 Demographic characteristics and average values of fatigue, depression and sleepiness scales of patient and control groups

	Myasthenia Gravis			Control			*p*
	Male[a]	Female	Total	Male[b]	Female	Total	
Gender (Female/Male)	22[c]	31	53	22[c]	31	53	1.000
Age	54.7 ± 10.8*	43.2 ± 13.0	48.0 ± 13.3	53.9 ± 10.2*	43.0 ± 13.6	47.6 ± 13.3	0.726
BMI (kg/m^2)	28.3 ± 3.9[c]	27.3 ± 6.3	27.7 ± 5.4	27.4 ± 5.0*	25.1 ± 5.7	26.1 ± 5.5	0.108
Education (Elementary/ High School)	14/8[c]	14/17	28/25	14/8*	9/22	23/30	0.286
FAS	22.27 ± 5.38[c]	24.55 ± 7.18	23.6 ± 6.54	20.04 ± 3.92[c]	20.58 ± 3.04	20.35 ± 3.40	***0.003***
FIS total	25.45 ± 24.73[c]	26.58 ± 22.70	26.11 ± 23.34	22.14 ± 15.40[c]	17.10 ± 10.80	19.19 ± 13.01	0.329
FIS cognitive	5.68 ± 6.82[c]	5.48 ± 6.15	5.57 ± 6.37	5.73 ± 5.15[c]	5.00 ± 3.44	5.30 ± 4.20	0.383
FIS physical	7.64 ± 6.65[c]	8.58 ± 6.73	8.19 ± 6.65	4.14 ± 3.52[c]	4.00 ± 2.76	4.06 ± 3.07	***0.001***
FIS social	12.14 ± 12.85[c]	12.52 ± 11.44	12.36 ± 11.93	12.32 ± 8.84[c]	8.10 ± 6.82	9.85 ± 7.93	0.543
BDI	7.05 ± 5.83*	11.87 ± 9.58	9.87 ± 8.51	6.31 ± 4.32[c]	5.64 ± 4.99	5.92 ± 4.69	***0.003***
ESS	3.18 ± 2.93*	5.68 ± 3.98	4.64 ± 3.76	3.54 ± 2.55[c]	4.29 ± 3.23	3.98 ± 2.97	0.519

Data are shown as mean ± standard deviation (SD)

Significant *p* values are indicated as bold italics

BMI body mass index; *FAS* fatigue assessment scale; *FIS* fatigue impact scale; *BDI* Beck depression inventory; *ESS* Epworth sleepiness scale

*$p < 0.05$

[a]MG male vs female

[b]Control male vs female

[c]Nonsignificant

Table 3 Comparison of fatigue, depression and sleepiness scales according to the clinical characteristics of the patients

	FAS		FIS total		BDI		ESS	
	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*
Ocular MG (*n* = 23)*	23.43 ± 6.37	0.054	18.30 ± 15.55	0.512	8.56 ± 5.27	**0.018**	4.60 ± 4.20	0.873
Control (*n* = 53)*	20.35 ± 3.40		19.19 ± 13.01		5.92 ± 4.69		3.98 ± 2.97	
Ocular MG (*n* = 23)*	23.43 ± 6.37	0.886	18.30 ± 15.55	**0.033**	8.56 ± 5.27	0.886	4.60 ± 4.20	0.731
Generalized MG (*n* = 30)*	23.73 ± 6.77		32.10 ± 26.60		10.86 ± 10.32		4.66 ± 3.46	
Anti-AChR (*n* = 24)*	22.45 ± 7.43	0.335	29.13 ± 19.91	0.182	9.29 ± 6.83	0.237	4.83 ± 4.14	0.805
Anti-MuSK (*n* = 5)*	27.40 ± 8.61		13.20 ± 12.31		18.20 ± 17.56		3.80 ± 3.96	
Seronegative (*n* = 22)*	23.59 ± 4.70		27.50 ± 28.24		8.04 ± 6.16		4.36 ± 3.41	
Early onset MG (*n* = 32)*	23.34 ± 6.76	0.757	27.34 ± 24.19	0.757	9.90 ± 7.10	0.471	5.09 ± 3.90	0.200
Late onset MG (*n* = 21)*	24.00 ± 6.32		24.24 ± 22.45		9.80 ± 10.50		3.95 ± 3.52	
Thymectomy (+) (*n* = 12)*	22.00 ± 5.52	0.317	36.67 ± 30.61	0.164	8.50 ± 7.85	0.306	4.75 ± 3.69	0.797
Thymectomy (−) (*n* = 41)*	24.07 ± 6.39		23.02 ± 20.18		10.26 ± 8.24		4.60 ± 3.83	
IS drug (+) (*n* = 31)*	22.87 ± 6.90	0.319	27.03 ± 21.89	0.316	9.35 ± 9.50	0.202	4.16 ± 2.64	0.849
IS drug (−) (*n* = 22)*	24.63 ± 5.99		24.82 ± 25.71		10.59 ± 7.03		5.31 ± 4.93	
Pyridostigmine (+) (*n* = 33)	24.66 ± 6.69	0.130	26.61 ± 26.65	0.846	11.30 ± 9.89	0.116	5.00 ± 4.19	0.379
Pyridostigmine (−) (*n* = 20)	21.85 ± 6.20		25.30 ± 17.11		7.50 ± 4.89		4.05 ± 2.92	
Steroid (+) (*n* = 22)	23.90 ± 5.39	0.778	24.14 ± 25.32	0.608	9.31 ± 6.66	0.696	5.04 ± 4.18	0.516
Steroid (−) (*n* = 31)	23.38 ± 7.32		27.52 ± 22.14		10.25 ± 9.70		4.35 ± 3.48	

Bold indicates $p < 0.05$ is the significance level

MG myasthenia gravis; *Anti-AChR* acetylcholine receptor antibody; *Anti-MuSK* muscle specific kinase antibody; *IS* ımmunosupressive drug

*Arithmetic mean ± standard deviation

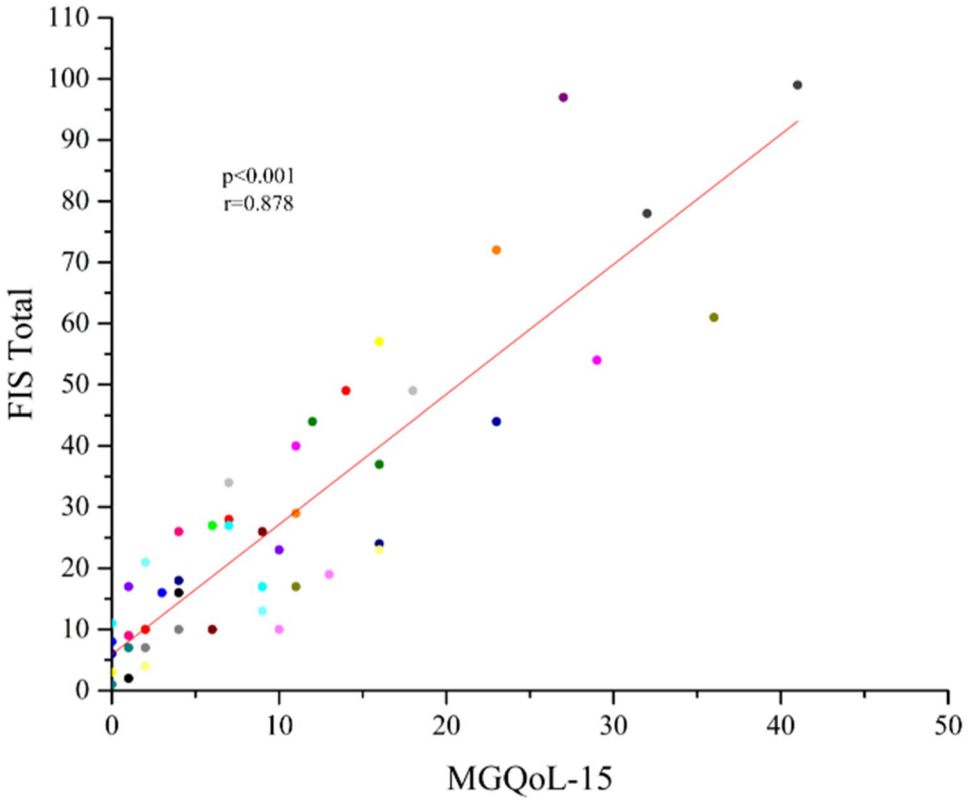

Fig. 1 Correlation of FIS total and MGQoL

($p < 0.001$, $r > 0.75$) (Fig. 1). FIS cognitive also showed a significant ($p < 0.001$) and moderately positive correlation ($r = 0.708$) with MG-QoL15. Significant weak positive correlation was observed between FIS physical and MG-ADL ($p = 0.041$, $r = 0.281$). FIS total, FIS cognitive, and FIS physical demonstrated a significant ($p = 0.012$, $p = 0.010$ and $p = 0.003$, respectively) and weak positive correlation ($r = 0.344$, $r = 0.350$ and $r = 0.396$, respectively) with MGC (Fig. 2). Whereas, a significant and moderate positive correlation ($p < 0.001$, $r = 0.691$), between FAS and BDI and a significant ($p = 0.002$) and weak positive correlation ($r = 0.422$) between FAS and ESS were observed. In addition, no correlation was found between fatigue, depression, sleepiness scales and age, duration of disease, educational status and vitamin D levels. All correlation analyzes are summarized in Table 4.

Discussion

This study confirms that ocular MG and patients with mild generalised MG, including patients in remission or in MM and therefore with no significant motor dysfunction, exhibit significant fatigue irrespective of muscle weakness and fatigability that negatively impacts their quality of life. This finding suggests that factors other than myasthenic muscle fatigability may have an impact on fatigue perception MG. Furthermore, we demonstrate a higher frequency of depression in myasthenic patients compared to controls, whereas no significant difference regarding daytime sleepiness.

In our study, the frequency of fatigue in patients with ocular and mild generalized MG was found to be higher according to FAS scores, when compared to the 44–56.1% frequency reported by the previous studies utilizing other scales in clinically more severe patients [19, 20]. It also supports the finding that fatigue is still an important cause of disability in patients even in complete remission or those who do not need treatment[20]. In contrary to the previous studies that reported a higher frequency of fatigue in females, our study revealed that females got higher scores with FAS and FIS, but these were not significant [4, 6]. In consistence with our study, Elsais et al. demonstrated no gender effect on fatigue in their patient group [20]. The lack of a significant difference in BMI between the patient and control groups reverses the belief that MG patients are heavier due to steroid treatment and therefore feel more tired by restriction of their physical activities [3]. As expected, the FIS-physical subscore was found to be significantly higher in the patient group, but there was no significant difference between patient and control groups in the FIS total score. However, in contrary to our study, Alekseeva et al. reported more social fatigue in patients with MG, but no difference in cognitive fatigue, compared to controls [4].

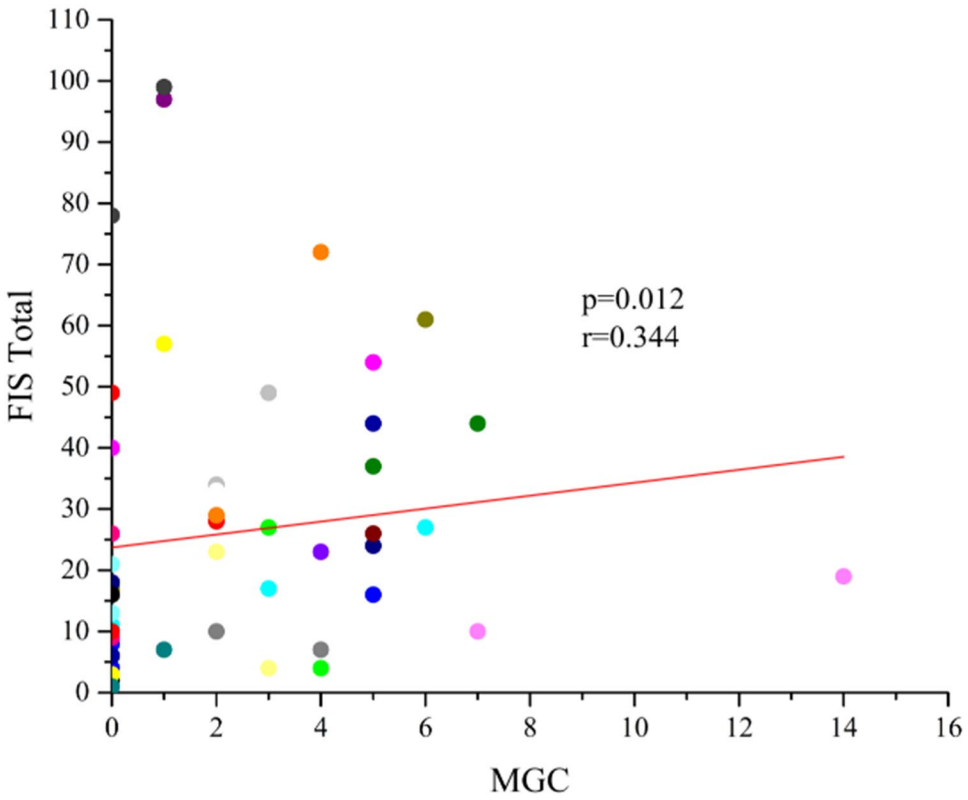

Fig. 2 Correlation of FIS total and MGC

Table 4 Relationship of fatigue scales with disease severity, quality of life, depression and sleepiness scales in MG patients

		MG-QoL15	MG-ADL	MGC	BDI	ESS
Spearman's rho*						
FAS	Correlation (*r*)	− 0.050	0.087	0.033	**0.691**	**0.422**
	p value	0.722	0.536	0.813	**0.000**	**0.002**
FIS total	Correlation (*r*)	**0.878**	0.244	**0.344**	− 0.136	− 0.026
	p value	**0.000**	0.078	**0.012**	0.331	0.852
FIS cognitive	Correlation (*r*)	**0.708**	0.257	**0.350**	− 0.113	− 0.208
	p value	**0.000**	0.063	**0.010**	0.419	0.134
FIS physical	Correlation (*r*)	**0.874**	**0.281**	**0.396**	− 0.080	0.079
	p value	**0.000**	**0.041**	**0.003**	0.571	0.574
FIS social	Correlation (*r*)	**0.815**	0.175	0.256	− 0.169	− 0.001
	p value	**0.000**	0.209	0.064	0.225	0.995

Bold indicates $p < 0.05$ is the significance level

*Spearman's correlation analysis

Activities of daily living profile

BDI Beck depression ınventory; *ESS* epworth sleepiness scale; *FAS* fatigue assessment scale; *FIS* fatigue ımpact scale; *MG-QoL15* myasthenia gravis quality of life-15; *MGC* myasthenia gravis composite scale; *MG-ADL* myasthenia gravis

In this study, patients with generalized MG had higher scores in all FIS subcategories, but only their FIS-total scores and cognitive fatigue scores were significantly higher, supporting the hypothesis that fatigue increases in proportion to the severity of the disease, in accordance with previous studies [6]. In addition, the cognitive fatigue of generalized patients also strengthens the opinion that cognitive fatigue is seen in MG in association with physical fatigue, and cognitive fatigue can also be affected by muscle fatigability[5, 21].

Our patients with ocular MG showed no significant difference in terms of FAS, FIS total and ESS, compared to controls, in consistence with a similar study conducted with FIS recently[4]. This finding might be due to the fact that our patient group with ocular MG was selected from patients with pure ocular symptoms lasting for at least 2 years, who were considered to have a reduced risk of generalization [6].

As in other chronic diseases, the patient group was more depressive in our study, in consistence with previous studies [19, 22]. In addition, the high correlation between FAS and BDI scores was compatible with the hypothesis that increased fatigue perception may be associated with more depressive symptoms. We found no significant difference in terms of daytime sleepiness between the patient and control groups, in contrary to studies pointing to increased daytime sleepiness in MG patients [23]. The correlation between FAS and ESS suggests that daytime sleepiness also contributes to the fatigue seen in some patients. In contrast to a previous study, no significant difference was found between ocular and generalized patients in terms of daytime sleepiness [19]. The reason could be that only the patients in remission or MM, so using low dose steroid or other drugs were recruited for our study.

Although the FIS total score was higher in patients with thymectomy, it wasn't statistically significant which may be due to the relatively low number of thymectomized patients. The relationship between thymectomy and fatigue was also investigated before [19]. As thymectomy is performed for people with generalised MG with positive AChR antibodies, these clinically worse patients were expected to have more fatigue.

When we compared the patients according to current medication (treatment with corticosteroids and other immunomodulatory drugs or pyridostigmine), there were no significant differences in terms of fatigue, depression and sleepiness, similar to a previous study [4]. It indicates that patients requiring immunomodulatory therapy benefit from the treatment and their fatigue or other non-motor symptoms are relieved. Low-dose corticosteroid therapy has been shown to be associated with depression [19]. Nevertheless, our study revealed no significant difference in terms of depressive symptoms in patients under corticosteroid therapy or not. In contrary to a previous study, we did not find any effect of antibody positivity on fatigue, depression and daytime sleepiness [19]. This could be a result of selecting the patients with full or nearly-full muscle strength in our study.

In this study, FIS and MGQoL-15 scores were found to be highly correlated. Thus, a similar finding was reported supporting that increased fatigue negatively affects patients' quality of life [6]. In another study, the quality of life of MG patients, apart from disease activity, was found to be negatively affected by depression, anxiety, and long

duration of illness [24]. In our study, the higher incidence of depression in the patient group suggests that depression may have a negative effect on the quality of life. The weak correlation between MG-ADL and FIS physical was thought to be mostly related to peripheral fatigue. In addition, the correlation of MGC, which is mostly considered as a motor assessment scale, with FIS total, cognitive and physical, also supports the sight that cognitive fatigue in MG is affected by muscle fatigue [21]. There was no correlation between vitamin D and MGC score, similar to the previous two studies [25, 26].

This study has some limitations. The most important one is the small sample size since only the patients with nearly full muscle strength were included in the study. However, by this way, a more specific group was selected and the effect of motor involvement on fatigue was minimized. At the same time, excluding many other comorbidities that can cause fatigue increased the homogeneity of the sample. Some of the patients were already under symptomatic or immunosuppressive treatment, so we could not evaluate the prevalence of fatigue without medication. Another limitation is that the vitamin D levels of the control group were not evaluated. The strength of our study is that, using multiple reliable scales, the non-motor symptoms of MG were comparatively evaluated in many aspects such as physical, social, cognitive, mood and sleep quality.

In conclusion, fatigue in MG is also seen in pure ocular or mildly generalized patients who are in remission, regardless of myasthenic muscle weakness and fatigability. More depressive symptoms in patients contribute to fatigue, and fatigue negatively affects the quality of life. Increasing the recognition of fatigue in clinical practice and taking precautions will guide the follow-up and treatment planning and also positively affect the quality of life in MG patients. Furthermore, investigating the etiopathogenesis of fatigue will provide further clarification of the pathophysiology of MG.

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Declarations

Conflict of interest No conflict of interest has been declared by the author.

Ethical approval The author declares that the research has been conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects." This study had been approved by the local ethical committee.

Informed consent Informed consent was obtained from all the participants.

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