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ORIGINAL ARTICLE

Quality of life in patients with MuSK positive myasthenia gravis

Milica Stankovic[1] · Stojan Peric[2] · Olivera Stojiljkovic Tamas[1] · Tamara Stankovic[3] · Ana Nikolic[2] · Dragana Lavrnic[2] · Ivana Basta[2]

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Abstract
It is believed that myasthenia gravis (MG) with antibodies to muscle-specific tyrosine kinase (MuSK) is the most severe form of the disease, especially in the first years of the disease. The aim of our study was to investigate quality of life (QoL) in a population of patients with MuSK MG compared to those with MG who have antibodies to acetylcholine receptor (AChR) in their sera. The study group consisted of 35 MuSK MG patients (28 females and 7 males), while the control group included 38 AChR MG patients matched for gender, age, and duration of the disease. SF-36 questionnaire was used to evaluate the health-related QoL. Following scales were also used: Hamilton's scales for depression and anxiety, the Multidimensional Scale of Perceived Social Support, and the Acceptance of Illness Scale. Physical domain scores of QoL were similarly affected in both MuSK and AChR groups, while mental domain and total SF-36 scores were even better in MuSK MG patients. Social support was better in the MuSK group (77.3 ± 9.3 vs. 70.6 ± 14.1, $p < 0.05$). SF-36 total score correlated with depression (rho = 0.54, $p < 0.01$), anxiety (rho = 0.49, $p < 0.01$), and MSPSS (rho = −0.35, $p < 0.05$), and depression was an independent predictor of worse QoL. Besides therapy of weakness, psychiatric treatment and different forms of psychosocial condition should be part of regular therapeutic protocols for MG. Adequate team work of health professionals and family can provide a healthy mental environment in which a MuSK MG patient would feel more comfortable in spite of the disease.

Keywords MuSK · Myasthenia gravis · Quality of life · SF-36 questionnaire · Depression · Social support

Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction presenting as muscular weakness and fatigability [1]. Autoantibodies to acetylcholine receptors (AChR) are present in 80–90% of the patients with generalized form of MG and in about 50% of those with the ocular form of the disease [2, 3]. In 40–70% of "seronegative" patients, antibodies to muscle-specific kinase (MuSK) are found [3, 4]. These patients usually have more severe form of the disease, normal thymus, and often require higher doses of immunosuppressive therapy. MuSK MG is also characterized by predominance of female patients, younger age at onset, and more frequent muscular atrophy of the affected muscles [5].

In MG patients, weakness and fatigue of different muscle groups cause significant limitations in daily activities that might affect patients' health-related quality of life (QoL). It is known that all chronic diseases can cause important psychosocial consequences [6–8]. However, many studies analyzed the physical limitations of the patients with MG [9, 10], usually without taking into consideration the psychological and social aspects. Some studies conducted on a large number of MG patients confirmed that QoL was affected, not only by severity of the disease, but also by mood changes, social support, and acceptance of the disease [6, 11, 12]. However, to our knowledge, no study of QoL in patients with MuSK MG exists at the moment.

The aim of this investigation was to analyze QoL in patients with MuSK MG comparing it with AChR MG patients matched for gender, age, and duration of the disease.

✉ Ivana Basta
ivanabasta@yahoo.com

[1] School of Medicine, University of Belgrade, Belgrade, Serbia

[2] School of Medicine, Neurology Clinic, Clinical Centre of Serbia, University of Belgrade, Dr Subotica Starijeg 6, 11 000 Belgrade, Serbia

[3] School of Medicine, University of Nis, Nis, Serbia

Patients and methods

The study was approved by the Ethical Board of the Neurology Clinic, Clinical Center of Serbia. All participants signed informed consent form to participate. The study group consisted of 35 MuSK MG patients (28 females and 7 males) examined in the Outpatient Unit of the Neurology Clinic, Clinical Center of Serbia, in the period from June 2012 to February 2013. Control group included 38 AChR MG patients (27 females and 11 males) matched for gender, age, and duration of the disease with the study group that were selected from the AChR subjects examined in the Outpatient Unit in the same period of time.

Diagnosis of MG was made according to the generally accepted criteria: fluctuating muscle weakness and fatigability, positive neostigmine test, positive decremental response for more than 10% during low-frequency repetitive stimulation, and/or increased jitter on single-fiber electromyography (SFEMG) [13]. Sera of these patients were analyzed for the presence of AChR antibodies by radio immune assay using commercial diagnostic test (CIS Biointernational), and for MuSK antibodies using the commercial kit (RSR Ltd, Cardiff, UK).

The form of MG at nadir of the disease and at the moment of investigation was determined according to the Myasthenia Gravis Foundation of America (MGFA) classification [13]. The patients were dichotomized into two groups regarding disease severity: mild form (MGFA I, IIA, IIB, and IIIA) and severe form (MGFA IIIB, IVA, IVB, and V) of MG [14]. Muscular weakness at the moment of investigation was assessed using the Quantitative Myasthenia Gravis Score (QMGS) [15]. MGFA was noted for every patient at two time points: at the peak of the disease and at the moment of the filling out of the questionnaires.

The degree of depression and anxiety were measured by the Hamilton Depression Rating Scale (HDRS) and the Hamilton Anxiety Rating Scale (HARS) [16, 17]. Presence of depressiveness was considered if HDRS was >9, while anxiety was suspected when HARS >18. Acceptance of the disease was analyzed using the Acceptance of Illness Scale (AIS), which has eight dichotomous statements. Higher value indicates worse acceptance [18]. Social support was determined by the Multidimensional Scale of Perceived Social Support (MSPSS) which includes three different types of support: support by partner, friends, and family members. Higher score indicates better support [19].

Serbian version of the SF-36 questionnaire was applied to assess QoL [20]. SF-36 comprises of eight life domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Two composite scores were calculated: physical composite score (PCS) and mental composite score (MCS), as well as total SF-36 score. Higher values indicate better QoL [21].

Depending on the type of variables, the differences between groups were analyzed using the following tests: Chi-squared test, Mann–Whitney *U* test, or Student's *t* test. ANOVA with Bonferroni post hoc tests was performed for comparisons between multiple groups. Multivariate linear regression analysis (enter method) was performed, including significant variables from the univariate model as independent variables and SF-36 total score as a dependent variable. *P* value ≤ 0.05 was considered for statistical significance and ≤ 0.01 for high significance.

Results

Sociodemographic, clinical, and psychosocial data of investigated patients are presented in Table 1. MuSK and AChR MG patients did not differ regarding the following parameters: sex, age, education, profession, or marital status ($p>0.05$). Severe form of MG at nadir was more common in MuSK MG patients (80.0 vs. 44.7%, $p<0.01$). Thymectomy was less frequently performed in MuSK group (25.7 vs. 63.2%, $p<0.01$). Thymectomy was always performed prior to analysis of anti-MuSK antibodies.

Autoimmune diseases were more frequently confirmed amongst AChR positive patients compared to the MuSK positive group (23.68 vs. 5.71%, $p<0.01$). Rheumatoid arthritis was the most frequent autoimmune disease in the MuSK positive group, while different types of thyroid diseases were the most common in the AChR positive group. Social support as measured by MSPSS was better in the MuSK group (77.3 ± 9.3 vs. 70.6 ± 14.1, $p<0.05$).

The results of the SF-36 questionnaire are presented in Table 2. Scores on GH, SF, and RE domains, as well as MCS and total SF-36 score were better in MuSK MG subjects compared to AChR group.

Using univariate analysis, it was found that total SF-36 total score correlated with depression (rho $=0.54$, $p<0.01$), anxiety (rho $=0.49$, $p<0.01$), and MSPSS (rho $=-0.35$, $p<0.05$). Due to the significant inter-correlation between depression and anxiety, anxiety was excluded from the multivariate model. The most significant predictor of worse QoL in MuSK MG cohort was the presence of depression (Table 3).

Discussion

Our results showed decreased QoL in patients with MuSK MG. Although our MuSK patients had more severe form of the disease at nadir compared to AChR ones, which is

Table 1 Demographic, clinical, and psychosocial characteristics of MuSK vs. AChR patients with myasthenia gravis

Parameter	AChR + (%)	MuSK + (%)	*p*
N	38	35	
Sex			
Male	28.9	20	0.38
Female	71.1	80	
Education			
Uneducated	0.0	5.7	0.34
Elementary school	10.5	17.1	
High school	68.4	54.3	
College/university	21.1	22.9	
Profession			
Physical work	18.4	5.7	0.12
Office work	26.3	22.9	
Intellectual work	26.3	14.3	
Unemployed	2.6	8.6	
Retired	26.3	48.5	
Marital status			
Married	71.1	60.0	0.36
Single	10.5	25.7	
Divorced	10.5	5.7	
Widowed	7.9	8.6	
MGFA at nadir (%)			
I	2.6	0	0.89
IIA	21.1	5.7	
IIB	31.6	14.3	
IIIA	5.3	0	
IIIB	31.6	51.4	
IVA	2.6	0	
IVB	2.6	17.2	
V	2.6	11.4	
MGFA at nadir (%)			
Mild	60.6	20.0	< 0.01
Severe	39.4	80.0	
Immunosuppressant drugs (%)	60.5	71.4	0.33
IVIg and/or PLEx (%)	2.3	20.0	0.06
Thymectomy	63.2	25.7	< 0.01
Other autoimmune diseases	23.7	5.7	0.03
Malignancies	5.3	2.9	0.62
Disease duration (mean ± SD, months)	107.2 ± 114.5	78.5 ± 76.5	0.40
MGFA at the moment (%)			
I	7.1	0	0.96
IIA	42.9	27.6	
IIB	32.1	55.2	
IIIA	3.6	3.4	
IIIB	14.3	13.8	
IVA	0	0	
IVB	0	0	
V	0	0	
MGFA at the moment (%)			
Mild	85.7	86.2	0.95
Severe	14.3	13.8	
QMGS (mean ± SD)	6.3 ± 4.2	5.9 ± 4.6	0.35
HARS (mean ± SD)	9.7 ± 8.1	12.4 ± 11.2	0.12
HDRS (mean ± SD)	8.5 ± 9.4	12.3 ± 12.1	0.07
MSPSS (mean ± SD)	70.6 ± 14.1	77.3 ± 9.3	< 0.05
AIS (mean ± SD)	20.3 ± 7.3	19.6 ± 9.5	0.74

Table 2 Results on SF-36 questionnaire in MuSK vs. AChR patients with myasthenia gravis

Quality of life	AChR+	MuSK+	*p*
PF	57.4 ± 28.6	64.9 ± 28.0	0.22
RP	38.2 ± 40.6	13.6 ± 44.2	0.15
BP	74.3 ± 28.7	72.1 ± 31.0	0.92
GH	49.9 ± 18.3	61.4 ± 25.5	0.04
VT	49.2 ± 24.0	56.9 ± 25.6	0.25
SF	58.9 ± 28.6	74.6 ± 29.9	0.01
RE	32.5 ± 43.5	66.7 ± 45.0	< 0.01
MH	56.7 ± 23.6	67.4 ± 23.8	0.05
PCS	53.8 ± 21.4	61.8 ± 25.6	0.13
MCS	49.4 ± 21.3	65.4 ± 25.9	< 0.01
Total SF-36	52.1 ± 22.2	64.7 ± 25.3	0.02

Table 3 Multiple linear regression analysis with total SF-36 score as a dependent variable (enter method)

Independent variable	Standardized coefficient beta	Significance
MSPSS	0.17	0.26
HDRS	0.84	< 0.01
	R^2 adjusted	0.54

in line with previous reports [5, 22–24], QoL was surprisingly better in MuSK positive group, particularly in mental domains. When compared to previous studies on QoL in MG patients conducted in our own and other European countries, our MuSK patients had a slightly better QoL [6, 25–27]. This could be at least partially explained by the fact that MuSK MG subjects had a good response on therapy—they had more severe disease at nadir, but similar severity to AChR MG at the time of testing. Comparing QoL of MuSK patients with other neurological patients from Serbia, it was

shown that QoL was worse in MuSK MG than in writer's cramp [28] and Wilson disease [29], and better than in torticolis [28], blepharospasm [28], multiple sclerosis [30], amyotrophic lateral sclerosis [31], muscular dystrophies, and chronic inflammatory demyelinating polyneuropathy [28–33]. Sub-analysis of individual SF-36 domains actually showed that QoL was equally reduced in physical domains in both MuSK and AChR patients. Furthermore, RP subscore was lower in MuSK MG although this did not reach a statistical significance. This is in line with the fact that MuSK positive MG has more severe phenotype at nadir than does AChR positive [5]. Some papers showed inferior score in the physical domains of QoL in comparison to the mental domains [34, 35].

In the analyzed group of MG patients, subscores on mental domains were significantly better in patients with MuSK MG compared to AChR ones. According to our results, one of the main reasons for this might be better social support in MuSK compared to AChR cohort. It seems that more severe phenotype during the course of the disease produces more empathy in partners, family members, and friends of patients. In a study by Raggi et al., two independent predictors of QoL in MG patients are defined: self-efficacy and tangible social support [36]. Others have shown that patients benefit from partner's backing in a common household, thus confirming our results [11, 27]. Having this in mind, it is clear that psychosocial support must be taken into account as a regular therapeutic intervention. Both patient and their families should be included to improve the therapy of MG and, consequently, the QoL in these patients.

It is of note that only 26% of MuSK patients and even 63% of AChR patients were thymectomised. This can partly explain the worse QoL in the group of AChR positive patients due to the invasive nature of thymectomy and possible postoperative complications. Further on, postoperative scarf may be of particular importance for patients' body image perception, especially taking into account a fact that majority of patients in our groups were females. Other studies regarding the influence of thymectomy on the QoL in MG patients are scarce. In previous studies, no difference could be found in the SF-36 score between thymectomised and non-thymectomised patients [6, 25]. Similar results were obtained in our AChR positive group (results not shown).

Another possible reason for better QoL in MuSK patients could be fewer concomitant diseases such as malignancies and autoimmune diseases compared to AChR-Ab positive patients. The literature remains scarce on this point as there are no studies that have questioned the impact of malignancies and other autoimmune diseases on the QoL in MG patients.

We performed a multiple linear regression analysis to identify prognostic value of independent factors (disease outcome, MSPSS, and HDRS) in the estimation of the total SF-36 score (as a dependent variable). Included independent variables explained 53.2% of the variability of total SF-36 score. The HDRS score was found to be an independent predictor of QoL in MuSK patients. This is in accordance with our previous study in MG [6]. Others have identified disease severity, depression, older age, and increased body mass index as independent predictors of QoL in MG patients [37]. It is possible that emotional aspects of patients with MG are deteriorated due to the everyday limitations caused by the disease. A consequence of these limitations may be anxiety and depression. Depression can also be a direct consequence of a poor acceptance of illness [36]. Providing professional treatment of depression in MuSK MG patients could lead to a significantly better QoL.

Our study has several limitations. We were unfortunately unable to compare our results with the general population of Serbia due to the lack of standard for the interpretation of the SF-36 test in our population. Comparing QoL results on MG patients from different countries is not completely adequate due to the different sociocultural backgrounds and different therapeutic approaches [35, 38]. Other limitations of the present study are the small sample size and cross-sectional design, although MuSK MG is a rare disease. Another limitation is the absence of the activities scale that certainly could contribute to the understanding of QoL in MuSK MG.

Conclusion

Despite MuSK MG is a more severe disease at nadir compared to AChR MG, MuSK positive patients had a better quality of life, especially in mental domains. SF-36 total score correlated with depression, anxiety, social support, and depression was an independent predictor of worse QoL. Thus, besides therapy of weakness, psychiatric treatment and different forms of psychosocial support should be part of a regular therapeutic protocol for MG. Adequate team work of health professionals and family can provide a healthy mental environment in which a MuSK MG patient would feel more comfortable in spite of the disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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