CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH MYASTHENIA GRAVIS: AN EXPERIENCE FROM UNIVERSITY CLINICAL HOSPITAL MOSTAR

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ABSTRACT

Introduction: Myasthenia gravis (MG) is an important health problem that affects significant number of patients. Proper understanding of the disease characteristics is important for adequate therapeutic approach.

Aim: The aim of our study was to determine clinical and laboratory characteristics of patients with MG that were cured at the University Clinical Hospital Mostar.

Subjects and methods: Data from the University Hospital Mostar Registry were used. In our study, we included all patients with MG (n=39), over the age of 18, regardless of gender, who regularly visit outpatient clinic. We analyzed following parameters: age, gender, clinical presentation, antibodies (AChR, MuSK), associated comorbidities, therapy, disease history, thymus pathology and applied treatment.

Results: MG occurred more often in female patients (58%). In female patients, MG occurred mostly at the age range from 30-70 years, compared to male patients where MG mostly occurred at the age range from 50-90 years. Generalized form of MG was present in 74.36% of patients, and 25.64% had the ocular form. Anti-AChR antibodies were positive in 78.38%, anti-MuSK in 5.41% and 16.22% of patients were seronegative. The prostigmine test was positive in 97.37% and negative in 2.63% of patients. Among the initial symptoms, the most patients had ptosis and fatigue, while dysarthria, dysphagia, and diplopia were less common signs.

Conclusion: Based on our study we can conclude that MG mostly affects older female population. The most of the patients had positive Anti-AChR antibodies and positive prostigmine test.

Keywords: myasthenia gravis, anti-AChR, anti-MuSK, pyridostigmine, corticosteroids

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INTRODUCTION

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction, where autoantibodies are directed against different components of the postsynaptic membrane in neuromuscular junction, resulting in characteristic weakness of the ocular, bulbar, respiratory muscles, and muscles of the trunk and limbs (1). Incidence and prevalence of this disease have significant geographical variations, but it is considered that MG incidence has increased worldwide over the last decades. Incidence rates have a bimodal distribution in women, with peaks around the age of 30 and 50, and in men, the incidence increases with age, with the highest rates between the age of 60 and 89, while in the fifth decade of life, women and men are equally affected (2). MG is caused by autoantibodies that bind to functional molecules on the postsynaptic membrane of the neuromuscular junction thus blocking normal transmission of nerve impulses. As many as 80% of patients have positive antibodies to acetylcholine receptors (AChR), a certain proportion of patients have positive antibodies to muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptors (LRP4), while minority of patients with MG do not have any detected positive antibodies (3-5). Two thirds of patients report isolated ptosis, diplopia, or both as their first symptoms (5,6). The vast majority of these patients will develop generalized weakness over the next 2-3 years with specific deterioration of muscle function during exercise and pronounced fatigue at the end of the day (1, 3). Although 15% of patients have only ocular symptoms, vast majority have a generalized form of MG, sometimes leading to myasthenic crisis, as a medical emergency (7). Myasthenia gravis is divided into subgroups according to the age at onset, clinical manifestations, presence of antibodies and thymus pathology, and accordingly there are some differences in the treatment of specific patients (3,5).

Fatigue is the main symptom of MG that fluctuate during the day, worsened by exertion and improved by rest, but also can be a consequence of steroids, apnea syndrome, depression, etc. (1,8). One of the main bulbar signs in severe forms of MG is facial muscle weakness, which can often be asymmetrical, with characteristic facial expression, called "myasthenic sneer" (9). The speech becomes more nasal and the difficulties in articulation are more pronounced leading to flaccid dysarthria and dysphagia. In some patients, airway obstruction occurs due to weakness of the vocal cords (10). Sometimes head-drop can occur, predominantly in male, and limb muscle weakness tends to be symmetric and proximal, leading to difficulty climbing stairs, getting up from chairs, and raising arms above their head. Although mostly proximal muscles affected, symmetrically or asymmetrically distal muscles can also be affected (2,11). In most patients with the generalized form, a reduced vital capacity and other respiratory parameters can be observed, regardless of the fact that there are no preceding signs of dyspnea (12).

Diagnosis of myasthenia gravis relay on a history, clinical neurologic examination and the result of the tensilone test or the prostigmine (neostigmine) test. A CT scan of the mediastinum and thymus,

if present, should be performed. Laboratory tests detect antibodies to acetylcholine receptors, anti-MuSK antibodies, anti-LRP4 antibodies. Anti-AChR and anti LRP antibodies can be demonstrated in enzyme-linked immunosorbent assay (ELISA), anti-MuSK radioimmunoassay (RIA). Even if laboratory tests for these antibody are negative, this does not rule out the disease (13). In this case, the diagnosis is based on the clinical picture, response to acetylcholinesterase inhibitors and electrodiagnostic tests (13).

The first line treatment for myasthenia gravis is oral acetylcholinesterase (AchE) enzyme inhibitors such is Pyridostigmine bromide (Mestinon), effective in cases of mild and moderate MG (14,15). However, their benefit is temporary and partial, so most patients eventually need immunosuppressive therapy, thymectomy and immunomodulatory therapy (15).

Until now, the number of patients with myasthenia gravis in the area of western Herzegovina is not known, and this was the focus of this research. Additional goal was to determine clinical and laboratory characteristics of these patients, in order for better understanding and treatment of these patients. The aim of this research is to determine the clinical characteristics of patients with myasthenia gravis (ocular and generalized form of the disease) and to determine the laboratory characteristics (seropositive and seronegative form of the disease). Additional goals are:

- Determine the distribution of patients with regard to gender
- Determine the age of onset of the disease and initial symptoms in patients with MG
- Determine the results of the prostigmine test and the neuromuscular junction test
- Determine thymectomy status in patients with MG
- Determine the therapy of patients with MG and the incidence of myasthenic crises.

SUBJECTS AND METHODS

Patients and study design

Patients diagnosed with myasthenia gravis, treated at the Department of Neurology of the University Clinical Hospital Mostar were included into our study. Criteria for inclusion were: all patients with MG over the age of 18, regardless of gender, who visit outpatient clinic for monitoring their clinical condition. Patients who were once registered, but no longer come for check-ups due to relocation or other personal reasons, were excluded.

This cross-sectional study was conducted retrospectively by examining the medical documentation of the University Hospital Mostar. The data were collected from the hospital information system (BIS). The parameters we considered are: age, gender, clinical picture, antibodies (AChR, MuSK, seronegative), associated comorbidities, therapy, family history and thymus pathology.

The study was approved by Ethical Committee of University Clinical Hospital Mostar.

Statistical analysis

The results of the statistical analysis are expressed in absolute and relative frequencies. The significance of the differences was tested with the $\chi 2$ test (in the absence of expected frequencies with Fisher's exact test). A $p<0.05$ was taken as statistically significant. Statistical analysis of the collected data was performed in IBM SPSS Statistics (version 25.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

A total number of 39 of patients with diagnosed myasthenia gravis were included in this research. MG occurred more often in female patients (58%) ($P<0.05$). In female patients, MG occurred mostly at the age range from 30-70 years, compared to men where MG mostly occurred at the age range from 50-90 years.

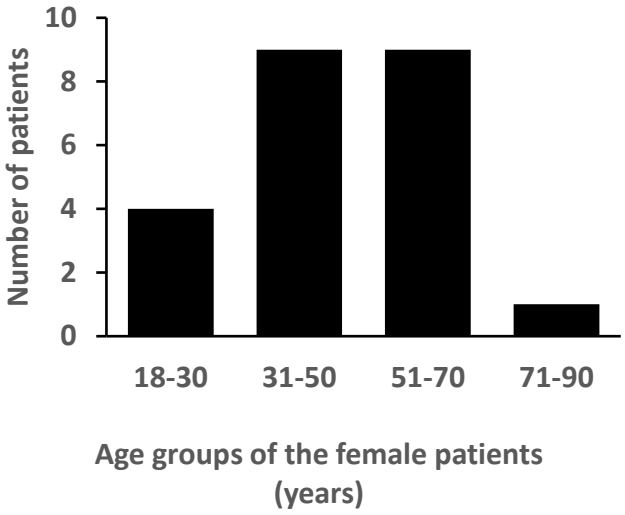

Figure 1. *The onset of the myasthenia gravis in female patients according to the age. On the figure the absolute number (N) of patients is shown.*

Figure 2. *The onset of the myasthenia gravis in male patients according to the age. On the figure the absolute number (N) of patients is shown.*

Only 2.86% of patients have a positive family history, and 97.44% does not have any relatives with MG. A large number of patients, 74.36% have the generalized form, and 25.64% have the ocular form ($p<0.05$).

AChR antibodies are positive in 78.38% patients with MG, MuSK antibodies in 5.41% and 16.22% of patients are seronegative ($p<0.05$).

Only 2.56% of patients had a positive neuromuscular junction test, while 97.44% were negative.

Only 7.69% were thymectomized, and 92.31% were not operated. So far, 17.95% of patients have had a myasthenic crisis, and 82.05% have more stable course of disease. In context of other autoimmune diseases, 74.36% of patients have no other diseases, 5.13% have hypothyroidism, 5.13% diabetes, 2.56% dermatomyositis, 5.13% rheumatoid arthritis, 2.56% have hypothyroidism and Crohn's disease, 2.56% asthma, 2.56% systemic lupus erythematosus (SLE) with myasthenia gravis.

Regarding medicamentous therapy, 58.97% of patients use Mestinon and prednisolone, 35.90% use only Mestinon, 2.56% use Mestinon, prednisolone and cyclosporine, and 2.56% use prednisolone and Imuran in combination (Table 1).

Table 1. *Clinical and laboratory characteristic of patients with MG*

	Form of MG					
	Generalized		Ocular		χ^2	p
	n	%	n	%		
Gender					1,085	0,264*
M	10	34,5	6	60,0		
F	19	65,5	4	40,0		
Family history					0	1*
Positive	1	3,4	0	0,0		
Negative	28	96,6	10	100,0		
MG antibodies					1,013	0,757*
AChR-p	23	79,3	6	75,0		
MuSK-p	2	6,9	0	0,0		
Negative	4	13,8	2	25,0		
Neuromuscular junction test					0	1*
Positive	1	3,4	0	0,0		
Negative	28	96,6	10	100,0		
Thymectomy status					0,137	0,556*
Operated	3	10,3	0	0,0		
Unoperated	26	89,7	10	100,0		
Myasthenic crisis					1,531	0,158*
Yes	7	24,1	0	0,0		
No	22	75,9	10	100,0		
Other autoimmune diseases					4,176	0,874*
No	21	72,4	8	80,0		
Hypothyroidism	2	6,9	0	0,0		
Diabetes	1	3,4	1	10,0		
Dermatomyositis	1	3,4	0	0,0		
Rheumatoid arthritis	1	3,4	1	10,0		
Hypothyroidism + Mb. Chron	1	3,4	0	0,0		
Asthma	1	3,4	0	0,0		
SLE	1	3,4	0	0,0		
Current therapy					3,696	0,303*
M	8	27,6	6	60,0		
M+P	19	65,5	4	40,0		
M+P+C	1	3,4	0	0,0		
P+I	1	3,4	0	0,0		

*Fisher's exact test

Most patients had ptosis as an initial symptom, followed by fatigue, dysarthria, dysphagia and diplopia (Figure 3).

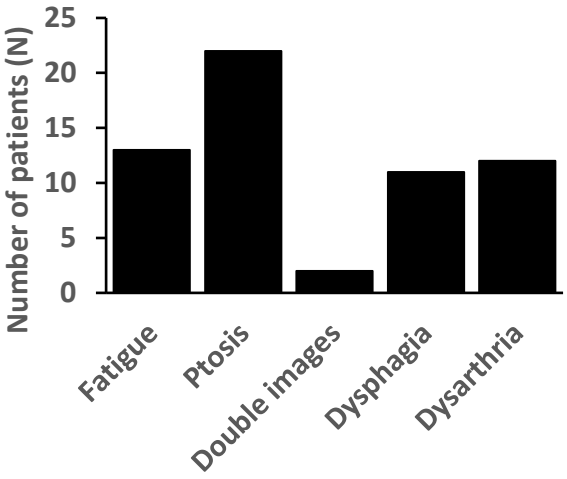

Figure 3. *Number of initial symptoms in patients with myasthenia gravis*

DISCUSSION

Our research provided important data about clinical and laboratory characteristics of patients with myasthenia gravis. Although myasthenia gravis is in the focus of numerous researches, data provided from the patients in this geographic area were not analyzed so far. In our research the majority of MG patients in Mostar are female, supporting most of other studies, such is the one conducted in Riyadh, Saudi Arabia (16). However, their subjects had a much earlier onset of the disease compared to the subjects in Mostar. Although we expected a larger number of younger patients with myasthenia gravis, our research was concordant with that from Korea, where an increase in the number of patients with myasthenia gravis in older age is being recorded (17). We found that the majority of patients in Mostar have a generalized form of the disease, and a smaller number have the ocular form of the disease, which suports the results reported in earlier study, where the most of ocular forms becomes generalized (2). The largest number of patients are positive for anti-AChR antibodies, followed by seronegative patients, and the fewest are patients who have positive anti-MuSK antibodies. Previously mentioned research in Riyadh, provided the similar results, although researchs in USA, South Africa and Norway list MuSK MG as the second most common form after AChR MG (17). A positive prostigmine test in the majority of our, but also patients from other international studies showed its clinical importance in diagnosis, as well as the response to therapy (18). As an aditional method for MG diagnosis, the neuromuscular junction test, was used, which on the other hand, was positive only in one patient with a generalized form of MG. We can conclude that almost all of our patients do not have pronounced pathological changes at the neuromuscular junction, which represents great limit of this test. This means that almost all MG patients in Mostar have a milder clinical

picture when it comes to muscle weakness and they respond well to therapy. In Norway, on the other hand, more patients had a positive neuromuscular junction test, which indicates a more severe clinical picture and more pronounced symptoms of muscle weakness (8). Myasthenic crises are an emergency condition in patients with MG which occured in only seven our patients and those of an older age. According to some research, patients who have other comorbidities and/or other autoimmune diseases more often have myasthenic crises. Older age is in favor of possible accompanying infections that can cause impairment of immunity and easier onset of myasthenic crisis. Research in Riyadh showed that significant number of patients had other autoimmune diseases, which is not the case with the results obtained in Mostar (16). Hypothyroidism, diabetes, dermatomyositis, rheumatoid arthritis, Crohn's disease, asthma and systemic lupus erythematosus were diagnosed in ten patients in University Clinical Hospital Mostar. Research conducted in Macedonia also confirmed these diseases as the most common in patients with MG, with an emphasis on thyroid disease. However, only one patient in Mostar had thyroid disease (18).

Most patients with MG undergo thymectomy for the purpose of treatment, although research conducted in USA and later in Baghdad showed that patients with a more severe clinical picture and pathohistological changes only achieved temporary remission after thymectomy (19, 20). Only 3 out of 39 of our patients were operated on. This indicates that patients in Mostar have a milder clinical picture and do not have significant pathohistological changes that require this surgical procedure compared to patients in other countries. Furthermore, it shows that the vast majority of patients in Mostar respond favorably to drug therapy and majority used a combination of Mestinon (pyridostigmine bromide) and prednisolone. This drug combination has also been shown to be successful in other clinical centers and is listed in global treatment guidelines (21). The fact that only one patient in Mostar, had a positive family history supports most of findings that myasthenia gravis appears sporadically and has no connection with family history. Of the initial symptoms, the most patients had fatigue and ptosis, followed by dysarthria and dysphagia, and the fewest had diplopia. Fatigue is the most common and non-specific symptom of the disease and is cited as the main symptom in the literature (2). Ptosis is the most common symptom in patients in Mostar, which corresponds to the clinical picture of MG, in the generalized and ocular form, mostly affecting the ocular muscles first.

CONCLUSION

In conclusion, the results of our research showed that the majority of patients with MG who come to our institution are elderly, with a generalized form of disease, a positive prostigmine test and a positive finding of anti-AcHR antibodies, as well as good response to therapy. These are the results of patients regularly monitored in a tertiary healthcare institution. We must also take into account the part of patients with periodic controls in other healthcare institutions, and those who are not yet included in the study in

order to achieve the most relevant epidemiological picture.

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KLINIČKE I LABORATORIJSKE ZNAČAJKE BOLESNIKA S MIASTENIJOM GRAVIS: ISKUSTVA IZ SVEUČILIŠNE KLINIČKE BOLNICE MOSTAR

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SAŽETAK

Uvod: Miastenija gravis (MG) je važan zdravstveni problem koji pogađa značajan broj bolesnika. Za adekvatan terapijski pristup važno je pravilno razumijevanje karakteristika bolesti.

Cilj našeg istraživanja bio je utvrditi kliničke i laboratorijske karakteristike bolesnika s MG koji su liječeni u Sveučilišnoj kliničkoj bolnici Mostar.

Ispitanici i metode: Korišteni su podaci iz Registra Sveučilišne kliničke bolenice Mostar. U naše istraživanje uključili smo sve bolesnike s MG (n=39), starije od 18 godina, bez obzira na spol, koji su na redovitim ambulantim kontrolnim pregledima. Analizirali smo sljedeće parametre: dob, spol, kliničku sliku, antitijela (AChR, MuSK), komorbiditete, terapiju, povijest bolesti, patologiju timusa i primijenjeno liječenje.

Rezultati: MG se češće pojavljuje kod bolesnica ženskog spola (58%). Kod ženskih bolesnica MG najčešća dob pojavljivanja je bila od 30-70 godina, u usporedbi s muškim bolesnicima kod kojih se MG većinom pojavila u dobi od 50-90 godina. Generalizirani oblik MG bio je prisutan u 74,36% bolesnika, a 25,64% imalo je okularni oblik. Anti-AChR protutijela bila su pozitivna u 78,38%, anti-MuSK u 5,41%, a 16,22% bolesnika bilo je seronegativno. Prostigminski test bio je pozitivan u 97,37%, a negativan u 2,63% bolesnika. Među početnim simptomima većina bolesnika imala je ptozu i umor, dok su dizartrija, disfagija i diplopija bili rjeđi znakovi bolesti.

Zaključak: Na temelju našeg istraživanja možemo zaključiti da MG najviše pogađa stariju žensku populaciju. Većina bolesnika imala je pozitivna Anti-AChR protutijela i pozitivan prostigminski test.

Ključne riječi: miastenija gravis, anti-AChR, anti-MuSK, piridostigmin, kortikosteroidi

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