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Analysis of The Clinical and Demographic Data of The Patients Diagnosed With Myastenia Gravis Followed-Up In Our Clinic

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ABSTRACT

Objective: The objective of this study is to evaluate the demographic characteristics as well as the clinical course, antibody, and electrophysiological characteristics of the patients diagnosed with Myastenia Gravis (MG) followed-up in our clinic.
Material and Method: The demographic characteristics as well as the radiological characteristics, clinical follow-ups, antibody results and electrophysiological characteristics of 99 MG patients followed-up in our Neuromuscular and Muscle Diseases Outpatient Clinic for a period of 5 years are examined.
Findings: The mean age of the patients was 44,38±15,2. The number of patients followed-up as isolated ocular MG was 22,22% (n=22). Acetylcholine receptor antibody (AntiAChRAb) was found positive in 53,54% (n=53) of the patients and thymus pathology (Thymoma + post-thymectomy thymic hyperplasia) was found in the thoracic tomography of 42,42% (n=42) of the patients.
Result: Although the pathologies in the development of MG are well known, in some cases, there may be some problems in the follow-up and treatment of MG patients. Therefore, detailed patient follow-up and long-term clinical monitoring is important in MG patients. There are some limitations due to the fact that this is a hospital-based study. An example of such limitations is the lack of data related to responses to the treatment. More extensive epidemiological studies on this matter will be more informative. Detailed patient file recording and administration of individualized treatments will provide positive results in the long term in MG patients who suffer from a chronic disease which progress with flare ups.

Keywords: Myastenia Gravis, Acetylcholine Receptor, Thymoma

Introduction

This is an autoimmune disease with muscle fatigue linked to the antibody developed against Ach receptors due to the deficit in Acetylcholine (Ach) receptors in postsynaptic membrane located in the neuromuscular junction. Weakness increases with fatigue and decreases at rest and this is a typical characteristic of the disease. (1,2). MG is more common in women compared to men.The course of this disease has attacks and recoveries. Typically, it starts with ocular symptoms and while the most frequent symptom is asymmetrical eyelid drooping (ptosis) and, additionally, it may be accompanied with double vision complaint. Subsequently, symptoms related to the bulbar muscles and extremity muscles are added and called as generalized MG (2,3). Anticholinesterase are used in symptomatic treatment. Immunosuppressive/immunomodulator drugs are used to treat the disease and achieve remission and thymectomy is performed. Intravenous immunoglobin (IVIg) and plasmapheresis is used in the treatment of attacks (4).

Muscle weakness is caused by an antibody-mediated immunologic attack against proteins in the post-synaptic membrane at the neuromuscular junction. The main antibodies that are frequently screened for in MG and cause disease development are antibodies against acetyl choline receptor (AChR) and muscle muscle-specific tyrosine kinase (MuSK). Antibody development against titin, ryanodine, collagen Q, cortactin and lipoprotein receptor-related protein 4 (LRP4) are also reported in MG. A group of patients lacking antibodies are called seronegative MG. Methods such as fatigue test and ice-pack test can be performed in diagnosing the disease. Anticholinesterase such as Edrophonium and Neostigmine can be used in the diagnosis of MG as pharmacological test. Electrophysiological tests such as repetetive nerve stimulation (RNS) and single fiber electromyography (SFEMG) are often

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used to diagnose MG.. Thymus gland plays a close role in the pathogenesis of MG.

MG is primarily diagnosed with clinical history and examination findings accompanied with electrophysiological and immunological supporting findings. Typical findings of the disease vary from patient to patient and can have atypical clinical presentations (5).

MG is a chronic autoimmune disease, and the clinical follow-ups and treatments of the patients can vary depending on various factors. Detailed patient follow-up is therefore important in patients with MG. In our study, we have aimed to present detailed clinical and demographic data of our patients followed-up in our clinic in the last 5 years diagnosed with MG accompanied with the literature.

Material and Method

This study was conducted in compliance with all the procedures, ethical code, and Helsinki pursuant to the Resolution of Van Yüzüncü Yıl University Hospital Clinical Research Ethics Committee (Date: 15.03.2023, Resolution No.: 04).

Demographic data of the patients followed-up in neuromuscular outpatient clinic of our hospital with MG diagnosis between the dates of 01.05.2018 to 01.06.2023, analysis of the number of patients with ocular, generalized, oculo-bulbar and bulbar involvement depending on the distribution of muscle weakness, antibody status, electrophysiological and radiological (thoracic tomography) characteristics and 99 MG patients whose primary treatment data are monitored were examined retrospectively.

The presence of MG clinical features and examination findings, elevated antibody levels (anti-AChR or anti-MuSK antibodies) and/or findings on electrophysiologic studies (≥10% decremental response on RNS) were used to establish the diagnosis of MG. Anti-AChR and anti-MuSK antibody tests were performed using the ELISA method. Patients with negative Anti-AChR and antiMuSK antibody results, however, having clinical histories, neurological examination findings, Neostigmine test, and RNS test consistent with MG were considered as seronegative MG. RNS test was performed in abductor digiti minimi muscle and nasal muscle. Myasthenia Gravis Foundation of America (MGFA) classification was used for clinical classification of MG patients at the time of diagnosis (6).

Statistical Analysis: Statistical analyses will be performed using SPSS software version 25.0. Conformity of the variables to normal distribution will be examined using the histogram graphics and Kolmogorov-Smirnov test. Mean, standard deviation, median, and min-max values will be used when presenting descriptive analyses. Results with P-value under 0.05 will be evaluated as statistically significant results.

Findings: 72 (72.73%) of the patients diagnosed with MG were female, and 27 (27.27%) were male. Mean age of the male patients was 51.41±15.7, and the mean age of the female patients was 41.75±14.23. (Table 1).

When the initial symptoms of the patients are examined in the clinical presentation, the number of patients with generalized MG symptoms were higher with 56 patients (56.57%), and the ocular form was the second most common with 26 patients (22.22%)

According to MGFA classification, highest number of patients was in class 2A (Table 1). According to MGFA classification, the severity of the disease had no statistically significant difference among female and male patients ($p>0,05$)

When the serum antibody values of the patients were examined, while Ach receptor antibody was tested positive in 53 patients (53.54%), anti-MUSK antibody was positive in 5 patients (5.05%). No antibody was detected in the serums of 41 patients (41.41%) (seronegative form).

In patient EMG, while the number of patients with decremental response in RNS was 40 (40.40%), the response was normal in 59 patients (59.60%) (Table-1). In probably thymic pathology screening in the Thoracic Computed Tomography, 35 patients (35.35%) had thymectomy with Thymoma diagnosis which was detected in the scan when they were first diagnosed, Thymoma was detected in 7 patients (7.07%), and thymic pathology was not detected in 57 patients (57.58%) (Table-1).

The number of patients in our cohort taking pyridostigmine as symptomatic treatment was 86 (86.87%). When the patients, taking cortisone, was examined, while 82 patients (82.83%) were on Methylprednisolone, there were 11 patients (11.11%) on Prednisolone. When other immunosuppressive treatment in the entire cohort was examined, there were 23 patients (76.77%) on Azathioprine, 4 patients (4.04%) on

Table 1: All Cohort Data

		n	%
Age Mean±s.s./Median (Min-Max)	Male	51,41±15,74	46 (25-75)
	Female	41,75±14,23	39 (18-75)
	Total	44,38±15,2	42 (18-75)
Sex	Male	27	(27,27)
	Female	72	(72,73)
Reception	Achr	53	(53,54)
	Seronegative	41	(41,41)
	Anti Musk	5	(5,05)
Thymic pathology	None	57	(57,58)
	Thymectomy	35	(35,35)
	Thymoma	7	(7,07)
Classification	Generalized	56	(56,57)
	Ocular	22	(22,22)
	Oculo-bulbar	15	(15,15)
	Bulbar	6	(6,06)
Metilprednisolon (Prednol)	No	82	(82,83)
	Yes	17	(17,17)
Piridostigmin (Mestinon)	No	13	(13,13)
	Yes	86	(86,87)
Azatioprin (İmuran)	No	76	(76,77)
	Yes	23	(23,23)
Mikofenolat Mofetil (Cellcept)	No	95	(95,96)
	Yes	4	(4,04)
Prednisolon (Deltacortil)	No	88	(88,89)
	Yes	11	(11,11)
Rituksimab (Mabthera)	No	98	(98,99)
	Yes	1	(1,01)
Methotrexate (MTX)	No	98	(98,99)
	Yes	1	(1,01)
Electromyography (EMG)	Normal	59	(59,60)
	Decrement	40	(40,40)
Myasthenia gravis foundation of America (MGFA)	Class 1	22	(22,22)
	Class 2A	31	(31,31)
	Class 2B	17	(17,17)
	Class 3A	15	(15,15)
	Class 3B	5	(5,05)
	Class 4A	7	(7,07)
	Class 4B	2	(2,02)

Mycophenolate Mofetil, 1 patient on Rituksimab, and 1 patient on Methotrexate.

Discussion

MG is an autoimmune disease characterized by muscle fatigue linked to the antibody developed against Ach receptors due to the deficit in Acetylcholine (Ach) receptors in postsynaptic membrane located in the neuromuscular junction. The incidence of MG is 7-23 millions/year, and the prevalence is 70-320 millions/year (7,8).

Most common occurrence in women is bimodal aged 20 to 30 and over 50, and over 50 in men (9).

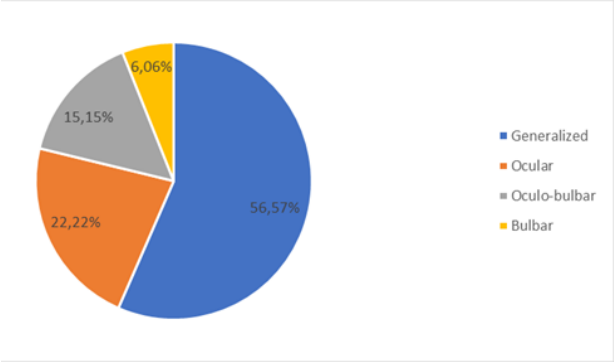

Fig.1. Clinical Classification

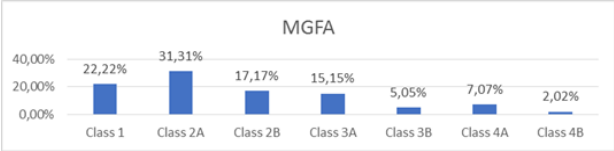

Fig.2. MGFA Classification

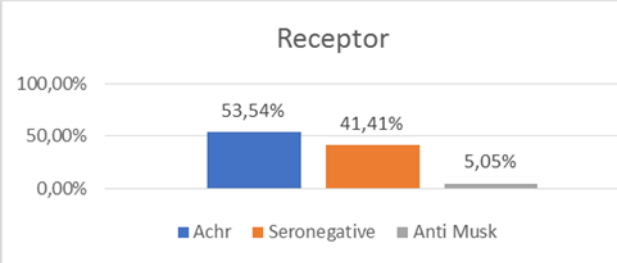

Fig.3. Antibody Analysis

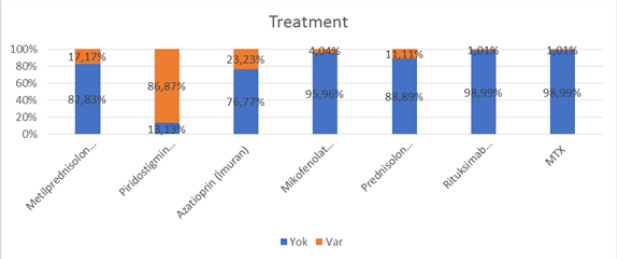

Fig.4. Patient Treatments

In our study, female and male patient ratio was evaluated as 72/27, similar to literature data. When analyzed according to age groups, it is noteworthy that our female patients are clustered in the 20-40 age group, while our male patients are clustered in the 40-50 age group and 60-70 age group. (Figure-5). Studies conducted in recent years indicate that MG is more common especially in the elderly. (10) Consistent with the literature, most of our patients were male patients older than 40 years with MG. Female patients were statistically significantly younger.

We had high number of clinically mild and moderate MG patients. We believe that the group of patients who come with characteristic disease findings and received early diagnoses is reflected in this statistic since our hospital has a Neuromuscular Disease Outpatient Clinic. We had a low number of patients with respiratory muscle weakness, severe enough to be intubated.

In various clinical studies, it has been reported that approximately 50% of patients present with ocular, 15% with bulbar and 5% with proximal muscle weakness (11). When our cohort was examined, our rates according to the distribution of initial symptoms, the number of patients presenting with generalized MG symptoms were higher, 56 patients (56.57%), the ocular form was the second most common with 22 patients (22.22%). (Figure-1).

While decrement response was observed in 40 patients in the EMG examination of our patients, in the repetitive nerve examination, 59 patients were normal. Single fiber EMG could not be studied on the patients, since single fiber EMG examination was not performed in the EMG laboratory of our center.

The treatment decision and the patient's follow-up interval should be appropriate for the individualized treatment approach in MG with a heterogeneous clinical course. Few patients can go into complete remission in MG. Considering the currently available clinical data and treatment preferences, care should be taken to select the most appropriate treatment for the patient. In our patient cohort, 35 patients were previously diagnosed with Thymoma and underwent thymectomy (Table-1). When patients are diagnosed with MG, treatment is often initiated with cholinesterase inhibitors in clinical practice. However, most patients may require the addition of immunosuppressive therapy. The data of the treatments received by our patients are given in Figure-4.

Although clinicians are experienced in MG patient follow-up, they have difficulties in treatment and follow-up due to some patient and disease-related problems. Therefore, detailed patient follow-up and long-term monitoring by the same clinician is important in MG patients. There are some limitations due to the fact that this is a hospital-based study. An example of such limitations is the lack of data related to responses to the treatment. More extensive epidemiological studies on this matter will be more informative. Since some of the newly defined antibody tests in MG disease were not performed in our hospital and since these tests were performed in the external center laboratories for a fee, these tests could not be

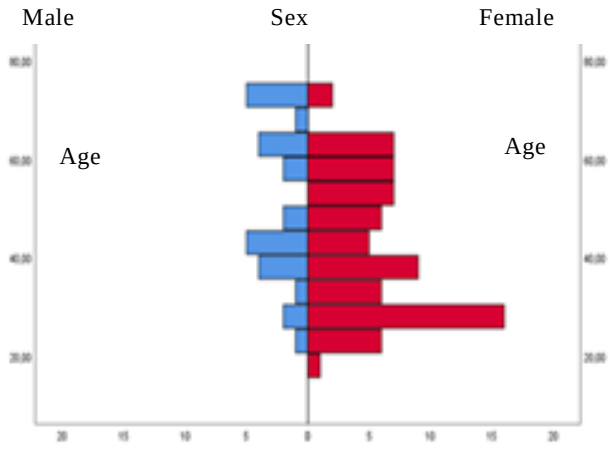

Fig.5. Age Distribution of Patients

examined in our patients. Another limitation of our study is that existing and newly identified antibodies could not be studied in seronegative MG patients for this reason.

Ethics Committee Approval: The study was conducted in compliance with all the procedures, ethical code, and Helsinki pursuant to the Resolution of Van Yüzüncü Yıl University Hospital Clinical Research Ethics Committee (Date: 15.03.2023, Resolution No: 04).

Patient Consent: Patient consent was not obtained since the study is a retrospective study.

Peer Review: Reviewed by editorial board and others not on the editorial board.

Financial Support: No financial support was received from any institution or person for the study.

Note: The data of the current study, in the form of a preliminary study evaluated with fewer patients, were presented as an oral presentation at the congress named "Uludağ Neurology Days" on 9-12 March 2023.

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