Outcomes and characteristics of myasthenia gravis: A 10-year retrospective cross-sectional study at King Fahad Medical City

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ABSTRACT

الأهداف: التحقيق في توزيع ضعف العضلات في الوهن العضلي والاستجابة العلاجية في كل فئة.

المنهجية: شملت الدراسة جميع مرضى الوهن العضلي الذين تم علاجهم في وحدتنا بين عامي 2010 و2020م. تم تسجيل البيانات الديموغرافية والسريرية والمصلي والفسيولوجية الكهربية والإشعاعية والنسيجية للمرضى. كما تم توثيق تفاصيل العلاج المعطى. تم تقسيم ضعف العضلات إلى: وهن بعضلات العين، ووهن بعضلات الفم والوجه والبلعوم، ووهن عام.

النتائج: اشتملت الدراسة على 147 مريضا، كان متوسط عمر المرضى المشمولين في هذه الدراسة 34.2±16.6 سنة. كان العرض الأكثر شيوعًا هو ضعف عضلات العين (57.1%). لم يكن هناك ارتباط كبير بين جنس المرضى والمجموعات الفرعية. تم اكتشاف وجود الأجسام المضادة ضد مستقبلات الاسيتيل كولين في 95.2%، 75%، و87% من المرضى الذين يعانون من الوهن العضلي العيني، وعضلات الفم والوجه والبلعوم، والوهن العضلي العام، على التوالي. كما تم اكتشاف الأجسام المضادة ضد مستقبل الكيناز العضلي في 20% من المرضى الذين يعانون من وهن بعضلات الفم والوجه والبلعوم. معظم المرضى الذين يعانون من وهن بعضلات العين (91.7%) ووهن بعضلات الفم والوجه والبلعوم (90%) أصيبوا بوهن عام في نهاية المتابعة، أظهر 82.6% و70.2% و57.5%من المرضى الذين يعانون من وهن عام، ووهن بعضلات العين، ووهن بعضلات الفم والوجه والبلعوم على التوالي استجابة جيدة للعلاج.

الخلاصة: كان العرض الأولي الأكثر شيوعًا هو وهن عضلات العين. معظم المرضى الذين يعانون من الوهن العضلي العيني، وعضلات الفم والوجه والبلعوم أصيبوا بوهن عام خلال فترة المتابعة. كان الجسم المضاد الذاتي الأكثر شيوعًا هو ضد مستقبلات الاسيتيل كولين. أظهر معظم المرضى الذين يعانون من الوهن العام، والعيني، وعضلات الفم والوجه والبلعوم ضعفًا تم التحكم فيه جيدًا في نهاية فترة المتابعة.

Objectives: To investigate the distribution of muscle weakness in Myasthenia gravis (MG) and the therapeutic response in each category.

Methods: This is a retrospective cross-sectional study included all MG patients presented to our clinic between 2010 and 2020. The demographic, clinical, serological, electrophysiological, radiological, and histopathological data of the patients were recorded. The details of the treatment administered were also documented. Muscle weakness was divided into: ocular, bulbar, and generalized.

Results: The mean age of the 147 patients included in this study was 34.2±16.6 years. The most common presentation was ocular MG (57.1%). There was no significant association between the gender of the patients and the MG subgroups. Antibodies against AChR were reported in 95.2%, 75%, and 87% of the patients with ocular, bulbar, and generalized myasthenia, respectively. Anti-MuSK antibodies were detected in 20% of the patients with bulbar weakness. Most of the patients with ocular (91.7%) and bulbar (90%) presentation developed generalized weakness. At the end of the follow-up, 82.6%, 70.2%, and 57.5% of the patients with generalized, ocular, and bulbar presentations, respectively demonstrated well-controlled weakness.

Conclusion: The most common initial presentation was ocular weakness. Most patients with ocular and bulbar presentation developed generalized weakness during the follow up period. The most frequently reported autoantibody was against AChR. Most patients with generalized, ocular, and bulbar presentation demonstrated well-controlled weakness at the end of the follow up period.

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Myasthenia gravis (MG) is an autoimmune disorder characterized by the presence of antibodies against neuromuscular junction receptors.[1] The yearly incidence of MG has been estimated to be between 7 and 23 new cases per million. However, with improved diagnosis, the prevalence is currently estimated between 70 and 320 cases per million.[2,3] The MG is classified into various subgroups according to the type of autoantibodies, epidemiology, clinical presentation, and comorbidities. This classification impacts the diagnosis, optimal therapy, and prognosis of MG. The most frequently targeted autoantigens in MG are the acetylcholine receptors (AChR),[4] which are found in more than 80% of the patients, and muscle-specific kinase (MuSK), which are found in about 4% of the patients.[5,6] MuSK-associated MG predominantly affects the cranial and bulbar muscles, and limb weakness is not common.[7] The degree of muscle weakness differs among patients and may affect the extraocular, bulbar, limb, and axial muscles.[8,9] Almost 60% of the patients present with ocular muscle weakness, and in 20% of patients, the disease is restricted to the eye.[10-12] However, studies have shown that eye weakness and generalized weakness in MG respond differently to different treatments; thus, it is essential to differentiate between the various phenotypes of MG for selecting treatment options and conducting clinical trials.[13,14]

Treatment protocols at leading medical centers are not based on results from well-controlled studies; as such, studies on MG are limited. The few studies that have been conducted have not considered the variations in therapeutic responses among subgroups.[5] In our research, we investigated the involvement of muscle weakness in seropositive MG (AChR and MuSK) patients and the therapeutic response in each category.

Methods. *Patients.* This is a retrospective cross-sectional study included all the MG patients who presented to the Neuromuscular Clinic at King Fahad Medical City, Riyadh, between 2010 and 2020. In all, 147 patients were enrolled for the study. Seropositive MG (AChR and/or MuSK) was diagnosed by a combination of variable muscular weakness and serum antibodies against AChR and/or MuSK. This study was approved by local ethical committee at King Fahad Medical City.

Clinical data. The demographic data of the patients, age at onset of MG, disease duration from the time of onset, number of severe respiratory distress requiring intensive care unite admission or exacerbations requiring hospitalization, results of autoantibody and nerve conduction tests, computed tomography (CT) of the chest, and histopathological examination of the thymus gland were recorded. The patients were questioned about ptosis, diplopia, dysarthria, weakness in chewing and swallowing, difficulty in breathing, weakness of the face and neck muscles and the limbs (hands, arms, and legs) during the first 6 months after the onset of MG. The details of the treatment administered in the previous 3 months were also documented. This included treatment with pyridostigmine, prednisone, and other immunosuppressants (azathioprine, mycophenolate mofetil, rituximab, cyclosporine, methotrexate, or cyclophosphamide). In addition, the use of intravenous immunoglobulin therapy (IVIg) or plasma exchange therapy during the course of the disease was also evaluated.

Muscle weakness was divided into 3 categories: ocular (ptosis or diplopia), bulbar (dysarthria, chewing weakness, swallowing weakness, or facial weakness), and generalized (a mix of ocular, bulbar, neck, respiratory, hand, arm, and leg weakness). Muscle weakness was evaluated at the time of the first presentation and in the last 3 months. Outcome was evaluated according to MG-activities of daily living (MG-ADL)[15] score (score ranges from 0 to 24) with higher score indicate higher level of MG severity. Patients who had no weakness (except mild weakness related to eyelid closure), with or without MG-specific therapy, for at least one year were considered as having controlled weakness.[6]

Statistical analysis. Data were analyzed with SPSS for Windows software version 21.0. Simple statistical tests were done for mean, standard deviation, frequency and percentage. T test, and ANOVA were used to compare age between male and female, and different MG subgroups respectively. Chi square and Fisher exact tests were used to compare proportions, with p-values of <0.05 considered significant.

Results. The mean age of the 147 patients included in this study was 34.2±16.6 years. Of the total patients, 72.8% were female. Male patients (48.3±17.0) were significantly (p=0.001) older than the female patients (28.9±13.0). The most common presentation was ocular MG (57.1%), which was followed by bulbar MG (27.2%). Patients with generalized MG were

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Table 1 - Demographic and clinical data of patients with myasthenia gravis. N=147

Characteristics	n (%)
Age in years Mean±SD	34.2±16.6
Disease duration in months Mean±SD	25.7±8.9
Gender	
Male	40 (27.2)
Female	107 (72.8)
Clinical presentation	
Ocular	84 (57.1)
Bulbar	40 (27.2)
Generalized	23 (15.6)
Anti AChR antibody	
Positive	130 (88.4)
Anti-MuSK antibody	
Positive	8 (5.4)
Double seronegative	11 (7.5)
RNS	
Decremental response	65 (44.2)
Normal	24 (16.3)
Not done	58 (39.5)
Treatment	
Pyridostigmine	14 (9.5)
Azathioprine	4 (2.7)
Pyridostigmine, prednisolone, with or without azathioprine	94 (63.9)
Pyridostigmine, prednisolone, with or without azathioprine, and one dose IVIg	10 (6.8)
Pyridostigmine, prednisolone, and mycophenolate	11 (7.5)
Pyridostigmine, prednisolone, with or without azathioprine, and monthly IVIg	14 (9.5)
Thymectomy	
Done	92 (62.6)
Not done	55 (37.4)
Treatment response	
Controlled	101 (68.7)
Not controlled	46 (31.3)
CT chest	
Prominent thymus	30 (20.4)
Thymoma	17 (11.6)
Normal	100 (68.0)
Histopathology	
Thymic hyperplasia	57 (38.8)
Thymoma	13 (8.8)
Normal	22 (15)
Clinical state at the end of follow up	
Ocular	7 (4.8)
Bulbar	4 (2.7)
Generalized	136 (92.5)
Family history of MG	
Positive	6 (4.1)
Negative	95 (64.6)
Not recorded	46 (31.3)

MG- Myasthenia gravis, AChR-acetylcholine receptors, RNS - repetitive nerve stimulation

significantly younger than patients with ocular (p=0.03) and bulbar presentation (p=0.043). Antibodies against AChR were detected in 88.4% of the patients and anti-MuSK antibodies in 5.4% of the patients, while 7.5% were double seronegative. Two patients, with bulbar presentation, had anti AChR, and anti-MuSK antibodies. Nerve conduction studies were performed on most (60.5%) of the patients, with decremental responses reported in 44.2 % of the patients. Only 6 patients (4.1%) had a family history of MG, all of them presented with ocular MG, and have antibodies against AChR, unfortunately, genetic testing was not available for any of them. The majority of the patients (63.9%) were treated by pyridostigmine with prednisolone and/or azathioprine, 6.8% required additional IVIg therapy once during the treatment course, while 9.5% needed monthly IVIg therapy. Azathioprine alone was used to treat 2.7% of patients, while 7.5% of patients required the replacement of azathioprine with mycophenolate mofetil, and 9.5% of the patients were treated with pyridostigmine only. Rituximab was used in 6 (4%) patients, three patients with anti-MUSK antibody MG, one with anti AChR antibody MG, and two with double seronegative MG. Fifty-three patients (36.1%) had exacerbations. The number of exacerbations ranged from one to 12 times. Thirteen patients (8.8%) had one exacerbation. Twenty patients (13.6%) were admitted to the intensive care unit (ICU) because of exacerbation. The number of ICU admissions for these patients ranged from one to 5 times. Two patients (1.4%) were admitted to ICU for 5 times. Most of the patients (68.7%) had well-controlled weakness associated with MG. Controlled weakness was more likely to be reported in patients with anti AChR antibodies (75.4%) compared to 25% of patients with anti-MUSK antibodies. The CT of the chest showed prominent thymus glands in 20.4% of the patients and thymoma in 11.6% of the patients. Thymectomy was performed in 62.6% of the patients. Histopathological examination confirmed thymus hyperplasia in 38.8% of the patients and thymoma in 8.8% of the patients. During the follow-up period (mean±SD 25.7±8.9) which ranges from 12 to 60 months, 92.5% of the patients had developed generalized weakness (**Tables 1 & 2**).

There was no significant association between the gender of the patients and the MG subgroups. Antibodies against AChR were reported in 95.2%, 75%, and 87% of the patients with ocular, bulbar, and generalized myasthenia, respectively. Anti-MuSK antibodies were not detected in any cases of ocular or generalized myasthenia, although they were detected in 20% of the patients with bulbar weakness. Two patients, with bulbar presentation, had anti AChR, and

Table 2 - Demographic and clinical differences between the myasthenia gravis subgroups.

Characteristics	Ocular n=84	Bulbar n=40	Generalized n=23	P-value
	n (%)			
Age Mean ±SD	35.6±16.1	36.1±19.2	25.6±10.2	0.03* 0.043**
Gender				
Male	25 (29.8)	11 (27.5)	4 (17.4)	0.497
Female	59 (70.2)	29 (72.5)	19 (82.6)	
Anti AChR antibody				
Positive	80 (95.2)	30 (75)	20 (87)	0.004
Anti-MuSK antibody				
Positive	0 (0)	8 (20)	0 (0)	0.000
Double seronegative	4 (4.8)	4 (10)	3 (13)	
NCS				
Decremental response	33 (39.3)	20 (50)	12 (52.2)	0.002
Normal	11 (13.1)	4 (10)	9 (39.1)	
Not done	40 (47.6)	16 (40)	2 (8.7)	
Treatment				
Pyridostigmine	7 (8.3)	2 (5)	5 (21.7)	0.000
Azathioprine	0 (0)	4 (10)	0 (0)	
Pyridostigmine, prednisolone, with or without azathioprine	65 (77.4)	18 (45)	11 (47.8)	
Pyridostigmine, prednisolone, with or without azathioprine, and one dose IVIg	2 (2.4)	8 (20)	0 (0)	
Pyridostigmine, prednisolone, and mycophenolate	2 (2.4)	6 (15)	3 (13)	
Pyridostigmine, prednisolone, with or without azathioprine, and monthly IVIg	8 (9.5)	2 (5)	4 (17.4)	
Thymectomy				
Done	55 (65.5)	18 (45)	19 (82.6)	0.009
Not done	29 (34.5)	22 (55)	4 (17.4)	
Treatment response				
Controlled	59 (70.2)	23 (57.5)	19 (82.6)	0.106
Not controlled	25 (29.8)	17 (42.5)	4 (17.4)	
CT chest				
Prominent thymus	19 (22.6)	11 (27.5)	0 (0)	0.003
Thymoma	9 (10.7)	8 (20)	0 (0)	
Normal	56 (66.7)	21 (52.5)	23 (100)	
Histopathology				
Thymic hyperplasia	35 (41.7)	13 (32.5)	9 (39.1)	0.000
Thymoma	9 (10.7)	4 (10)	0 (0)	
Normal	11 (13.1)	1 (2.5)	10 (43.5)	
Clinical state at the end of follow up				
Ocular	7 (8.3)	0 (0)	0 (0)	0.003
Bulbar	0 (0)	4 (10)	0 (0)	
Generalized	77 (91.7)	36 (90)	23 (100)	
Serology				
Positive	82 (97.6)	38 (95)	20 (87)	0.104
Negative	2 (2.4)	2 (5)	3 (13)	

AChR - acetylcholine receptor, MuSK - muscle-specific kinase, RNS - repetitive nerve stimulation, IVIg - intravenous immunoglobulin, CT - computed tomography, *Significant difference between ocular and generalized MG, **Significant difference between bulbar and generalized MG

anti-MuSK antibodies. At the same time, 10%, 13%, and 4.8% of the patients with bulbar, generalized, and ocular presentation were seronegative, respectively. Most of the patients with ocular (91.7%) and bulbar (90%) presentation developed generalized weakness at the end of the follow-up period. Regarding thymic lesions, all

cases with generalized presentation had normal chest CT scans with no evidence of thymic lesions, patients with ocular presentation had evidence of thymoma (10.7%) and prominent thymus (22.6%) on the CT scans. Patients with bulbar presentation had evidence of thymoma (20%) and prominent thymus (27.5%) on the CT scans. Histopathological examination revealed the presence of thymoma in 10.7% and 10% of the patients with ocular and bulbar presentations, respectively and the presence of thymic hyperplasia in 41.7%, 32.5%, and 39.1% of the patients with ocular, bulbar, and generalized presentation, respectively. At the end of the follow-up, 82.6%, 70.2%, and 57.5% of the patients with generalized, ocular, and bulbar presentations, respectively demonstrated well-controlled weakness (**Table 2**).

Discussion. The present study included 147 patients with MG. There were more female patients than male patients, and they were significantly younger than the male patients. Our results were in accordance with previous studies conducted in the same region.[4,6,16] Although MG has traditionally been considered a disease of young women (under 40 years of age), in recent years, its incidence has increased in both sexes with age.[17] Currently, patients are classified into 2 groups according to the age of onset, i.e., early-onset MG (onset before 50 years) and late-onset MG (onset after 50 years).[18,19] Early-onset MG is more common in women, whereas late-onset MG is slightly more common in men.[20] A recent study reported that in men, MG occurs more frequently in the elderly population. In contrast, it usually occurs at a younger age in female patients.[21]

The most common weakness that the patients presented with was ocular weakness, followed by bulbar weakness. Generalized weakness was the least common. A previous studies reported ocular presentation as the most common presentation of patients with MG,[4,5] and more than 80% of the patients reporting it at presentation.[4,22]

Patients with ocular and bulbar presentations were significantly older than patients with generalized presentation. Similar results were reported by De Meel et al[22] who found that compared to patients with neck, limb, or respiratory involvement, patients with ocular, or bulbar, presentation were older at the time of disease onset with a higher proportion of males. In another study, about one-third of MG patients below the age of 30 years reported limb weakness as the first presentation, while 15–20% of the patients complained of weakness in the arms, hands, or legs as the first presenting symptom.[23]

Antibodies against AChR were the most frequently reported autoantibodies in the population, and are commonly associated with ocular and generalized presentation. In contrast, anti-MuSK antibodies were significantly associated with bulbar presentation. Previous studies have reported anti-AChR antibodies in about 71–85% of the patients with MG[4,6,16,21,24,25], and 54.7-68.2% of the patients with ocular MG.[6,16,25] In agreement with our results, Guptill et al.[7] reported that anti-MuSK antibodies were present in 17% of the patients who presented with pure bulbar weakness, in 26% of the patients who presented with oculobulbar weakness, but only in 9%,[25] and 20.8%[4] of the MG patients regardless of the type. We did not observe anti-MuSK antibodies in any of the patients with ocular presentation, which is consistent with the results of previous studies.[25,26]

The most common treatment modality was pyridostigmine with prednisolone, with or without azathioprine, especially in patients with ocular presentation. A relatively large number of patients with bulbar presentation required additional IVIg or treatment with a more potent immunosuppressant. A recent study reported that pyridostigmine was the most prescribed medication for almost 94% of patients with MG, followed by glucocorticoids for 61.8% and azathioprine for 60.4% of the patients.[4] A comparable results were reported also by Alanazy,[6] in this study patients were divided into early onset MG and late onset MG, prednisolone was prescribed for 80% and 85% respectively while pyridostigmine was prescribed for 57.3% and 80% respectively. Heterogeneity in treatment response and outcome has been reported for different types of MG, depending on the clinical presentation, autoantibody status, and presence of comorbidities.[25] Regardless of the autoantibody status, treatment strategies are classified into symptomatic, immunosuppressive, and antibody-depleting therapies.[27] Pyridostigmine is the most common symptomatic treatment used.[28,29] However, compared to patients with anti-AChR antibody-associated MG, patients with anti-MuSK antibody-associated MG do not respond as well to pyridostigmine.[30,31] In MG, glucocorticosteroids and azathioprine are the first-line drugs for immunosuppression. Other immunosuppressive drugs such as cyclosporine, methotrexate, and mycophenolate mofetil can be used in case of contraindications, intolerance, or insufficient clinical response. The IVIg and plasmapheresis can also be used in certain situations.[27] Prednisone was used by 43.1% of patients in a recent study, followed by azathioprine (25%), mycophenolate mofetil (7.3%), methotrexate (1.3%), plasma exchange or IVIg treatment (14.7%), and rituximab (11.6%).[25]

In the present study 36.1% of the patients had at least one exacerbation during follow up period, and 13.6% required ICU admission. Nearly the same frequency of exacerbation and ICU admission was reported by previous studies conducted in the same region.[4,6]

Most patients with ocular and bulbar presentation developed generalized weakness during follow-up. It has been reported that about two-thirds of ocular MG patients progress to generalized disease within 2–3 years of disease onset.[32] In contrast, only about 10-27.6% of the patients sustain purely ocular presentation.[5,10, 25] The onset of ptosis or diplopia as an isolated symptom was predictive of early progression, in contrast to the concurrent development of ptosis and diplopia.[33]

In this study patients with generalized and ocular presentation responded well to different medical treatment modalities. It has been reported that different MG phenotypes respond differently to various treatment modalities.[13,14,34] A randomized clinical trial found that patients with pure ocular MG did not respond as well to IVIg compared to those with generalized MG.[35] The role of IVIg in anti-MuSK MG is not known,[36] it had been reported that clinical improvement is more common with plasma exchange than IVIg,[37] other study suggested that IVIg treatment may be an effective therapeutic option for anti-MuSK antibody-positive MG, with a potentially long-term effect.[38] Over 70% of the patients with generalized MG and anti-AChR antibodies appeared to improve with treatment with acetylcholinesterase inhibitors such as pyridostigmine.[39] However, fewer than 33% of the patients with ocular MG[34,40] and anti-MuSK MG[28] appeared to benefit from the same treatment. Some patients with anti-MuSK antibodies respond negatively to acetylcholinesterase inhibitors and display deteriorating clinical symptoms, including worsening of weakness, frequent cramp, and fasciculations, and decreased therapeutic responsiveness to acetylcholinesterase inhibitors[37,41,42] which may indicate an abnormal sensitivity to cholinergic agents, which limits the use of acetylcholinesterase inhibitors in this group of patients.[31] Almost 80% of the patients with generalized MG showed remission after immunosuppressive treatment, and a similar response was observed in ocular MG patients.[43] In the present study, anti-MuSK antibodies were not detected in any of the patients with ocular or generalized MG, which could explain the relatively good response of these patients to treatment, as compared with patients with bulbar presentation, for whom anti-MuSK antibodies were detected in 19.1% of the patients.

Although this study had the benefit of a 10-year follow-up period and provided information on treatment response, clinical course, and potential outcomes for each subcategory of MG patients, it was limited by the small number of patients because the neuromuscular unit was a newly developed unit in our institute. A larger investigation with a large number of patients with diverse subtypes of MG is recommended.

In conclusion, MG was found to be more frequent in young female patients. Ocular weakness was the most prevalent initial symptom. During the follow-up period, the majority of patients with ocular and bulbar presentation acquired widespread weakness. The AChR autoantibody was the most commonly reported autoantibody. At the end of the follow-up period, the majority of patients with generalized, ocular, and bulbar presentations had well-controlled weakness.

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