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Characterization of patients with ocular myasthenia gravis — A case series

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ABSTRACT

Ocular myasthenia gravis (OMG) is sometimes difficult to diagnose and is probably both under-diagnosed and misdiagnosed. We studied the epidemiological parameters, relevant serology, electromyographic (EMG) findings, and the relationship between OMG and thymoma, thymus hyperplasia and other autoimmune disorders compared to generalized MG (GMG) in a case control study of 133 patients with MG (32 patients with OMG and 101 patients with GMG). The proportion of OMG among all MG patients was relatively high (24.1%). It affected more males than females and its onset was at an older age. Although anti-AChR Ab was detected in fewer OMG patients compared to GMG patients, the rate of positive serology in OMG patients was higher than previously reported. Male OMG patients had a higher positive serology rate than female OMG patients. OMG patients tended to have less supportive EMG evidence of neuromuscular disorder. Female OMG patients had higher rates of thymus hyperplasia and higher rates of other autoimmune disorders than males.

Diagnosing MG in patients with solitary ocular manifestation may be difficult due to lower rates of paraclinic supportive tests. Awareness of the characteristics of OMG is important in order to avoid delayed or misdiagnosis of MG and to prevent avoidable iatrogenic complications.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease against the post-synaptic components of the neuromuscular junction (NMJ) of the striated skeletal muscle. The disease is mediated by antibodies (Ab) against the acetylcholine receptor (AChR) in the majority of the patients [1,2] and in some patients by Ab against muscle specific kinase (MuSK) that play a role in AChR clustering or Ab against low-density lipoprotein receptor-related protein 4 (LRP4) that forms a complex with MuSK [3]. The disease manifestation includes muscular weakness that tends to fluctuate. Some patients have ocular weakness (ptosis and/or ophthalmoparesis) as the only symptom of the disease along its entire course, and they are designated as having ocular MG (OMG), while the majority of the patients also have weakness of extraocular muscles and they are designated as having generalized MG (GMG) [4]. The reasons for the predilection of MG to involve ocular muscles are not entirely clear, but they appear to be related to the facts that the extraocular muscles have less prominent synaptic folds, fewer postsynaptic AChRs and smaller motor units, in addition to being subject to high-firing frequencies [5].

About 90% of individuals who have the ocular form for more than 2 years will remain in the OMG subgroup [6]. The age at onset, serology, association with thymus pathology or with other autoimmune disorders and response to therapy may differ in patients with OMG from those with GMG [7]. Since fewer OMG patients have detectable anti-AChR Ab in their sera compared to GMG patients, it is more difficult to diagnose seronegative patients with only ocular manifestations as having MG. In this observational case control study, we sought to study the epidemiology, and the clinical, serology, and electromyographic (EMG) characteristics of individuals diagnosed as having OMG and to compare those parameters with those patients with GMG.

2. Methods

2.1. Study design and participants

We retrospectively reviewed all files of patients diagnosed as having MG who attended the Neuro-immunology Clinic at the Tel Aviv Medical Center, Tel Aviv, Israel from January 1, 2006 until December 31, 2014.

Abbreviations: OMG, ocular myasthenia gravis; SP, seropositive; SN, seronegative; AChR, acetyl choline receptor; MuSK, muscle specific kinase; RSEMG, repetitive stimulation electromyography; SFEMG, single fiber electromyography.

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Table 1
Gender and age at myasthenia gravis onset.

a	GMG n = 101	OMG n = 32	*P* value
Females: males	54:47	11:21	0.047
Age at onset (years, mean ± SD, range)	55.2 ± 20.9, 15–90 y	60.1 ± 13.6, 31–80 y	0.136
Age at onset > 50 years (%)	55.4%	78.1%	0.038
b	Females	Males	*P* value
Age at OMG onset (years, mean ± SD, range)	55.0 ± 16.8, 33–80 y	62.5 ± 11.5, 31–78 y	0.221
Age at GMG onset (years, mean ± SD, range)	50.5 ± 23.0, 15-84 y	60.9 ± 16.9, 21–90 y	0.014

Abbreviations: GMG, general myasthenia gravis; OMG, ocular myasthenia gravis; SD, standard deviation.

The MG diagnosis was determined by history, physical examination, single-fiber EMG (SFEMG), repetitive-stimulation EMG (RSEMG), edrophonium testing and Ab serology of anti-AChR Ab or anti-MuSK Ab. In addition to compatible history and physical examination findings, the diagnosis of MG was established when at least 1 of the 3 following types of tests was supportive for MG: serology, SFEMG and/or RSEMG, and edrophonium assessments, as well as when other possible diagnoses were ruled out.

Included in the study were 133 patients diagnosed as having MG with disease duration of more than 2 years. The patients were categorized into 2 groups, OMG and GMG. All the patients underwent serology tests for anti-AChR Ab (tested by radioimmunoassay), and those who were negative were also tested for anti-MuSK Ab (tested by radioimmunoassay). All the serological assays were done in the same laboratory. They all underwent SFEMG and all GMG patients underwent also RTEMG that were done at the time of investigation for the possible diagnosis of MG. Some of them also underwent edrophonium test. All the study patients had either a chest computerized tomogram or a magnetic resonance imaging scan of the chest, and those that were detected with suspected thymic tissue underwent thymectomy. The pathology results determined whether there is thymic hyperplasia, thymoma or non thymic tissue.

2.2. Data analyses

The study was approved by the local Helsinki Committee. The significance of differences between groups was examined by Student's *t*-test for parametric parameters and by the Chi-Square test or Fisher Exact test for non-parametric parameters. Data are presented as mean ± standard deviation for age at the time of disease onset or as the number of patients for the other studied variables.

3. Theory

We hypothesized that as compared to patients with GMG, patients with OMG differ in epidemiology and electromyography features as well as in the rates of association with thymic pathology and with other autoimmune disorders.

4. Results

4.1. Rate of OMG

One-hundred and thirty-three MG patients (66 females and 67 males) were included in the study. Of them, 101 patients had GMG and 32 had OMG. We compared epidemiological parameters, serological results, EMG findings and the association with thymus hyperplasia and thymoma as well as with any other existing autoimmune disorders between the OMG patients and the GMG patients. OMG was diagnosed in 24.1% of our study cohort, and tended to occur more in males (n = 21) than in females (n = 11), unlike the trend in GMG which occurred in fewer males (n = 46) than females (n = 55), $P = 0.047$.

4.2. Age of OMG onset

The age at disease onset tended to be older among the OMG patients (60.1 ± 13.6 years) compared to the GMG patients (55.2 ± 20.9 years, $P = 0.136$). A higher proportion of OMG patients was older than 50 years at disease onset (n = 25, 78.1%) compared to GMG patients (n = 56, 55.4%, $P = 0.038$) (Table 1a). There were gender differences in the age at MG onset: there was a trend towards a difference in the OMG group (females: 55.0 ± 16.8 years, males: 62.5 ± 11.5 years, $P = 0.221$), while the difference between the females (50.5 ± 23.0 years) and males (60.9 ± 16.9 years) reached a level of significance ($P = 0.014$) in the GMG group (Table 1b). An age of onset until 50 years was found in 36.4% of females vs. 14.3% of males in the OMG patients and in 52.7% of the females and 26.1% of the males in the GMG patients.

4.3. Rates of thymic involvements

No significant differences were found in the rates of thymoma, thymus hyperplasia and non-thymus pathology between the OMG patients (2, 3 and 27 patients, respectively) and the GMG patients (6, 22 and 73 patients, respectively) (Table 2a). Thymus hyperplasia was found only among females (3 out of 11 patients) in the OMG group ($P = 0.029$). There was a similar trend in the occurrence of thymus hyperplasia in the GMG patients (16 out of 55 female patients vs. 6 out of 46 male patients, $P = 0.051$) (Table 2a). Thymoma and thymus hyperplasia were more common in the GMG patients with age at disease onset ≤ 50 years (6 and 18 patients, respectively) than in the GMG patients with age at disease onset > 50 years (none with thymoma and 4 patients with hyperplasia, $P = 0.007$ and $P < 0.001$, respectively). There was no difference in the occurrence of thymoma or thymus

Table 2
The relation of thymus pathologies with clinical manifestations of myasthenia gravis and gender.

a	GMG n = 101	OMG n = 32	*P* value
Thymoma	6	2	1.00
Thymus hyperplasia	22	3	0.188
b	Females	Males	*P* value
Thymus hyperplasia in OMG	3/11	0/22	0.029
Thymus hyperplasia in GMG	16/55	6/46	0.051
c	Age at onset ≤50 years	Age at onset >50 years	*P* value
Thymomas in OMG	1/7	1/25	0.395
Thymomas in GMG	6/46	0/55	0.007
Thymus hyperplasia in OMG	2/7	1/25	0.113
Thymus hyperplasia in GMG	18/46	4/55	>0.001

Abbreviations: GMG, general myasthenia gravis; OMG, ocular myasthenia gravis.

Table 3
The relation between serologic findings and clinical manifestations and gender with myasthenia gravis onset.

a	GMG	OMG	*P* value
Positive anti-AChR Ab	84/101	23/32	0.160
Positive anti-MuSK Ab	3/101	0/32	1.000
Double seronegative	22/101	3/32	0.192
Positive anti-AChR Ab, females	42/55	5/11	0.018
Positive anti-AChR Ab, males	42/46	18/21	0.669
b	Females	Males	*P* value
Positive anti-AChR Ab in OMG	5/11	18/21	0.035
Positive anti-AChR Ab in GMG	42/55	40/46	0.175

Abbreviations: GMG, general myasthenia gravis; OMG, ocular myasthenia gravis.

hyperplasia according to the age at disease onset among the OMG patients (Table 2c).

4.4. Serologic and electromyographic rates

The proportion of anti-AChR Ab detection tended to be lower among OMG patients (23 out of 32) than GMG patients (85 out of 101, $P = 0.160$) (Table 3a). This resulted from the lower proportion of anti-AChR Ab detection among OMG females (5 out of 11) vs. OMG males (18 out of 21, $P = 0.035$) (Table 3b) and vs. GMG females (42 out of 55, $P = 0.018$) (Table 3a). Anti-MuSK Ab was detected in 3 patients, all of whom were GMG females. Only 24 of the 32 OMG patients had increased jitter on their SFEMGs compared to 91 of the 101 GMG patients ($P = 0.039$) (Table 4a). Among the GMG patients, 42 had decrement in RSEMG (1 of them normal jitter in SFEMG). This resulted mainly from the lower rates increased jitter in the SFEMGs of OMG males (13 out of 21) vs. OMG females (11 out of 11, $P = 0.029$) (Table 4b) and vs. GMG males (44 out of 46, $P < 0.001$) (Table 4a).

4.5. Co-morbidity with other autoimmune diseases

Co-morbidity of MG with other autoimmune disorders is well documented. In our cohort of 133 MG patients, 7 had Hashimoto's thyroiditis, 3 had Grave's disease, 2 had polymyositis, 2 had systemic lupus erythematosus and 1 had rheumatoid arthritis. The other autoimmune disease was diagnosed before the diagnosis of MG in eight patients, at the same time in three patients and after MG diagnosis in four patients. The proportion of these other autoimmune disorders did not differ between OMG patients (5 patients) and GMG patients (10 patients) (Table 5a). As expected, those autoimmune disorders tended to occur more among the female patients in both patient groups: specifically, they were present in 4 out of 11 OMG female patients vs. 1 out of 21 OMG male patients, $P = 0.037$, and in 8 out of 55 female GMG patients vs. 2 out of 46 male GMG patients, $P = 0.106$ (Table 5b). Surprisingly, these co-morbidities tended to occur more in patients with an older age at MG onset among the GMG patients: 9 of the 56 patients with disease onset when they were older than 50 years had co-morbidities compared to only 1 of the 45 patients who were ≤50 years of age at disease onset ($P = 0.039$). There was no similar difference among the OMG patients (Table 5c).

5. Discussion

In this study, we investigated epidemiological, clinical, serological, and electromyographic characteristics of patients with OMG compared to those with GMG. Since many patients with newly diagnosed ocular-only manifestations will eventually have the generalized form of MG within the first year or two, it was advised to reserve the OMG classification for patients with ocular-only manifestations that extended beyond 2 years from disease onset [8]. We therefore selected patients who had been diagnosed as having MG for at least 2 years.

The rates of the types of clinical manifestations of MG are known as being different between different ethnic populations. In our cohort, the proportion of OMG among all MG patients was relatively higher (24.1%), and they were older at disease onset than that reported in other Caucasians by Grob et al. [9] but closer to the rate of 28% reported in a Chinese population [10]. Similar to the findings in previous studies, our OMG patients tended to be males, with a lower proportion of positive anti-AChR Ab levels in their sera compared to GMG patients. However, the ratio of seropositivity of anti AChR Ab was 71.9%, which is higher than what was reported before to be around 50% and less in OMG patients [9,11,12]. The relatively high ratio of OMG patients who were seropositive to anti-AChR Ab in our group was mainly due to the high ratio of seropositive male OMG patients. Furthermore, our OMG patients tended to have less supportive EMG evidence for a neuromuscular disorder in their SFEMGs. This finding was observed mainly in the male OMG patients. This is a low sensitivity of SFEMG than is usually accepted, especially the rate in our OMG patients. Nevertheless, such rates had been reported before [8] and reflect the non-uncommon possibility of negative SFEMG in OMG patients, especially in male patients.

The age of MG onset tends to be older in OMG group, mainly due to the older age of onset among OMG male patients that were the majority among OMG patients. The average age of onset of female patients was older than was previously reported [9], which resulted from the fact that the age of MG onset in female tend to cluster in 2 age periods: early onset and late onset, while in male late onset was much more frequent than early onset.

Table 4
Electromyographic findings according to the clinical manifestations and gender.

a	GMG	OMG	*P* value
Positive SFEMG	91/101	24/32	0.039
Positive SFEMG, females	47/55	11/11	0.333
Positive SFEMG, males	44/46	13/21	<0.001
b	Females n = 11	Males n = 21	*P* value
Positive SFEMG, OMG	11/11	13/21	0.029
Positive SFEMG, GMG	47/55	45/46	0.037

Abbreviations: SFEMG, single fiber electromyography; GMG, general myasthenia gravis; OMG, ocular myasthenia gravis.

Table 5
The occurrence of other autoimmune disorders among myasthenia gravis patients according to the clinical manifestations, gender and age at disease onset.

	GMG n = 101	OMG n = 32	*P* Value
Other auto immune disorders	10	5	0.372
	Females	Males	*P* value
Other autoimmune disorders, OMG	4/11	1/21	0.037
Other autoimmune disorders, GMG	8/55	2/46	0.106
	Age at onset ≤ 50 y	Age at onset > 50 y	*P* value
Other autoimmune disorders, OMG	1/7	4/25	1.000
Other auto immune disorders, GMG	1/45	9/56	0.039

Abbreviations: GMG, general myasthenia gravis; OMG, ocular myasthenia gravis.

The OMG and GMG patients in our cohort had similar rates of thymoma, in opposition to the claim by others that thymoma is more frequent in GMG patients [13]. Female patients tended to acquire MG at a younger age and tended to have thymus hyperplasia and co-morbidities consisting of other autoimmune disorders more than male MG patients. The latter association tended to occur in female patients with a relatively older age at MG onset. This interesting observation can be related to the incomplete understanding of the general biological basis for the tendency to have autoimmune diseases. Many genetic, epigenetic and environmental factors play a role in determining the extent of such tendencies [14]. Immune dysregulation of the self-tolerance mechanisms is probably a result of the presence of adequate factors that lead to the tendency to have MG as well as co-morbidity with other autoimmune diseases [15]. The association of hyperplasia of the thymus and female gender has been previously described in MG [16], however, to the best of our knowledge, it has not been described as being specifically associated with OMG as well.

OMG patients sometimes have various characteristics that relate to gender. There are usually fewer female OMG patients than male OMG patients, they are less likely to have positive serology tests for anti-AChR Ab, and they tend to have higher rates of thymus hyperplasia and other autoimmune disorders than males. Since the therapeutic approach is usually milder for OMG patients compared to GMG patients [6,17], it is important to know the manifestations of this MG subtype. There are a number of difficulties in diagnosing OMG. Besides the need to wait at least 2 years before defining a given patient as most probably having OMG, these individuals have fewer serological and electrophysiological findings to arrive at a definitive MG diagnosis, especially the males who comprise the majority of OMG patients. Since the rate of positive edrophonium test findings is sometimes lower in OMG than in GMG [18,19], patients that exhibit only ocular symptoms, such as ptosis and ophthalmoparesis, may be underdiagnosed due to the lack of supportive evidence.

6. Conclusions

Awareness of the possible clinical, serological, and epidemiological parameters and of the EMG findings characteristic of OMG may prevent delayed diagnosis and misdiagnosis and spare patients from the consequences of both as well as those of avoidable iatrogenic complications [20,21]. OMG is more common in males with later age of disease onset and a relatively high frequency of seropositive anti AChR Ab. Furthermore, the diagnosis of OMG does not make the search for thymoma, thymic hyperplasia and for other autoimmune diseases to be avoidable.

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