Keywords: Ocular myasthenia gravis
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Anti acetyl choline antibody
Thymoma
Thymic hyperplasia

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.
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 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 (n = 101) and in 52.7% of the females and 26.1% of the males in the GMG patients, respectively.

| Table 1 | Gender and age at myasthenia gravis onset. |
|---------|------------------------------------------|
|         | GMG n = 101                               |
|         | OMG n = 32                                |
| a       |                                         |
| females: males | 54.47                                    |
| age at onset (years, mean ± SD, range) | 55.2 ± 20.9, 15–90 y                     |
| age at onset > 50 years (%) | 55.4%                                    |
| b       |                                         |
| age at OMG onset (years, mean ± SD, range) | 55.0 ± 16.8, 33–80 y                     |
| age at GMG onset (years, mean ± SD, range) | 50.5 ± 23.0, 15–84 y                     |

### Table 2

The relation of thymus pathologies with clinical manifestations of myasthenia gravis and gender:

|         | GMG n = 101       | OMG n = 32       | P value |
|---------|-------------------|-------------------|---------|
| Thymoma | 6                 | 2                 | 1.00    |
| Thymus hyperplasia | 22      | 3                 | 0.188   |
| Thymus hyperplasia in OMG | 3/11       | 0/22              | 0.029   |
| Thymus hyperplasia in GMG | 16/55       | 6/46              | 0.051   |
| 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; SD, standard deviation.
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. GMG 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, 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).

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 than what was 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 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 3
The relation between serologic findings and clinical manifestations and gender with myasthenia gravis onset.

|                | 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        |

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

|                | 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     | \(<0.001\)   |

### Table 5c
The proportion of anti-AChR Ab detection 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. GMG 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).

### Abbreviations:
- GMG, general myasthenia gravis; OMG, ocular myasthenia gravis.
Since the rate of positive edrophonium test especially the males who comprise the majority of OMG patients.


electrophysiological

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 ophthalmoplegia, 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, thyptic hyperplasia and for other autoimmune diseases to be avoided.

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