

Diagnostic yields and clinical features of ocular myasthenia gravis

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Abstract

To investigate clinical features and diagnosis process of ocular myasthenia gravis (OMG) in ophthalmology department.

A total of 36 patients with ptosis or diplopia who had follow-up for at least 3 months between March 2016 and December 2019 were included in this study. Clinical symptoms of patients and the test results were analyzed. According to the positivity of serologic test, these patients were divided into 2 groups (confirmed OMG and possible OMG with relief of symptoms after antimuscarinic treatment) for comparison.

Ptosis was present in 12 (33.33%) patients, diplopia was present in 14 (38.89%) patients, and both ptosis and diplopia were present in 10 (27.78%) patients. Acetylcholine receptor auto-antibody (AChR Ab) was positive in 14 (38.89%) of 36 patients and ice test was positive in 15 (71.43%) of 21 patients with ptosis. Unequivocal response to pyridostigmine was observed in 31 (86.11%) patients. For seropositive cases, AChR Ab titer was significantly higher in the group with 2 clinical symptoms than that in the 1 clinical symptom ($P=.011$).

This study presents the usefulness and diagnostic validity of antimuscarinic treatment for OMG, especially seronegative OMG, with detailed symptom analysis.

Abbreviations: Ab = antibody, AChR Ab = acetylcholine receptor auto-antibody, GMG = generalized myasthenia gravis, OMG = ocular myasthenia gravis, PD = prism diopters, RNST = repetitive nerve stimulation test.

Keywords: diplopia, myasthenia gravis severity, ocular myasthenia gravis, ptosis, pyridostigmine

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction, it is characterized by exertional weakness and fatigability.^[1] This disease generally begins with ocular symptoms (ptosis and/or diplopia) in up to 85% of patients and extends to other muscles (generalized MG, GMG).^[2] For this reason, patients with suspected MG are often referred to

an ophthalmologist for a first visit. Among them, 15% of patients belong to a localized subgroup called, ocular MG (OMG) which affects extraocular muscles, levator palpebrae, and orbicularis oculi.^[3] However, the diagnosis of OMG is often challenging based on clinical findings because of OMG should be considered in the differential diagnosis of any pattern of painless, unilateral or bilateral, pupil-sparing ophthalmoplegia with or without ptosis. In most patients, MG can be caused by auto antibodies to the muscle nicotinic acetylcholine receptor. However, such auto-antibodies are not detected in 50% of patients with OMG, the positivity is much lower than with GMG (80%). Other diagnostic tests including Jolly test, ice test, rest test, and neostigmine test have various sensitivities and specificities.^[1,4-8] Some patients show unequivocal improvement after antimuscarinic regimen trial, although they show no positive findings in tests.^[9] Hence there is no gold standard diagnostic test available for MG, especially for OMG. Although there are many studies about GMG, most of these studies have mentioned about long-term prognosis, presented as a conversion rate to GMG. Researches on diagnostic yields of OMG are relatively rare. Herein, we describe clinical features and diagnostic yields of routine tests for OMG suspects without generalized symptom. Further, we subdivided them according to diagnostic tests positivity (patients with unequivocal improvements after antimuscarinic treatment were included) and symptoms (one of ptosis or diplopia, both of them). Results will help clinicians perform proper diagnostic process and offer adequate treatment options when they meet patients with ptosis or diplopia.

2. Methods

This study was approved by the Institutional Review Board of Samsung Changwon Hospital (Changwon, Republic of Korea),

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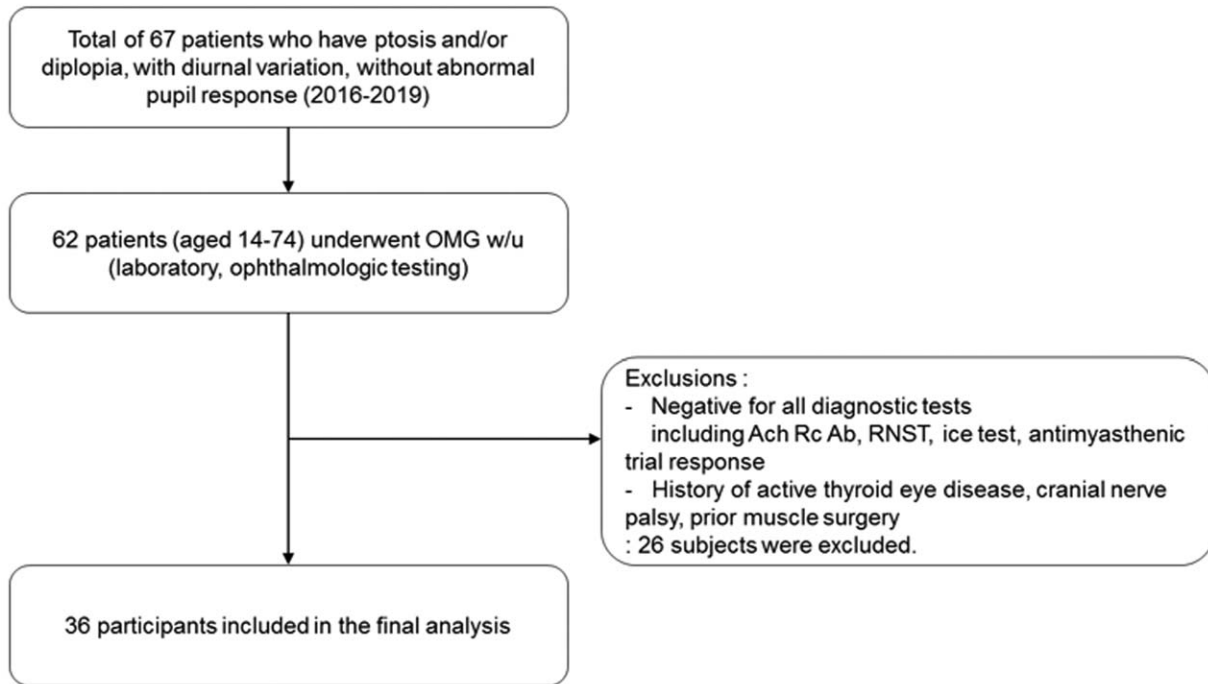


Figure 1. A flowchart describing the study participants included in the final analysis.

conducted according to tenets of the Declaration of Helsinki. Informed consent was obtained from all patients and all identifiable personal information of patients would be anonymized. We retrospectively reviewed medical records of adult patients complaining of ptosis or diplopia with diurnal variation and fatigue between March 2016 and December 2019 at Samsung Changwon Hospital. Inclusion criteria were: those who age 18 years or more, 3 months or more of follow-up, fulfilling our definition of OMG (the presence of ptosis, diplopia or both), and at least one of the followings: positive acetylcholine receptor auto-antibody (AChR Ab) test, significant response in repetitive nerve stimulation test (RNST), unequivocal clinical response to a longer acting acetylcholinesterase antagonist (pyridostigmine) and positive ice test. RNST was performed using the method of Oh et al^[8] in 5 muscles: the abductor digiti minimi and flexor carpi ulnaris after ulnar nerve stimulation, the orbicular oculi and nasalis after facial nerve stimulation, and the trapezius after spinal accessory nerve stimulation. The compound muscle action potential (CMAP) was recorded in each tested muscle. There was improvement in pyridostigmine treatment; however, some patients had taken oral steroids as needed for further treatment. AChR-binding Ab titers were analyzed using a radioactive isotope-based radioimmunoassay (RIA) and titers of ≥ 0.02 nmol/L were regarded as abnormal. Exclusion criteria were: history of active thyroid eye disease, cranial nerve palsy and known strabismus, previous extraocular muscle surgery or GMG occurrence at the onset of symptoms. GMG was defined as the development of symptoms or clinical findings such as dysphagia, dysarthria, dyspnea, or weakness of the face, jaw, neck, or extremities. Although 67 patients were screened, but 36 patients who fulfilled the inclusion criteria were included in this study (Fig. 1). Demographics and clinical characteristics were obtained from

medical records, including patient's age of onset, sex, ocular symptoms (ptosis and/or diplopia), presence of thyroid disease, presence of other autoimmune disorders, presence of thymic abnormalities (i.e., thymic hyperplasia or thymoma), ice test, pyridostigmine response, and treatment of steroid.

2.1. Ophthalmic evaluation and symptom severity assessment

At the first visit, patients underwent ophthalmologic assessment, including slit-lamp, measurement of horizontal/vertical deviation, and fundus photography. Angles of horizontal and vertical deviation were measured using alternating prism cover test at distant primary position for diplopia patients while ice test was performed for ptosis patients. In diplopia patients, degree of deviated angle was described by prism diopters (PD). The ice test was judged positive if there was an improvement of marginal reflex distance from at least 2.0 mm after the ice test. Mild ptosis was defined as 2 mm or less, moderate ptosis was defined as 2 to 4 mm, and severe ptosis was defined as 4 mm or more lower than the desired upper eyelid level.

2.2. Subgroup analysis

Subgroup analysis was performed based on their laboratory testing results and number of initial symptoms. Based on laboratory test results, subjects were classified into 2 groups: confirmed OMG, patients with positive AChR Ab or RNST; and possible OMG, patients presenting unequivocal clinical response to pyridostigmine without positive AChR Ab or RNST. Based on the number of symptoms, subjects were divided patients into 2 groups: both ptosis and diplopia (2 clinical symptoms), and ptosis or diplopia only (1 clinical symptom).

2.3. Statistical analysis

All statistical analyses were conducted by an independent statistician using a commercially available statistical package (STATA V.14.0; Stata Corporation, College Station, TX, USA). Demographic differences between groups were compared using Mann–Whitney *U* test, Fisher exact test, and Pearson’s Chi-Squared test. A *P* value of less than .05 was considered statistically significant.

3. Results

3.1. Baseline clinical characteristics of patients for OMG

A total of 36 patients (18 males and 18 females) were included in this study, and mean length of follow-up was 10.1 ± 13.3 months after initial visit. The average age at OMG onset was 50.39 ± 13.57 years (range: 19–74). At the initial visit, ptosis was present in 12 (33.33%) patients, diplopia was present in 14 (38.89%) patients, and both ptosis and diplopia were present in 10 (27.78%) patients. In 22 patients with ptosis, 9 patients presented with mild ptosis, 9 patients presented with moderate ptosis, 4 patients presented with severe ptosis, and 3 patients had bilateral ptosis. In 24 patients with diplopia, 18 (75.0%) patients had horizontal deviation and 13 (54.17%) patients had vertical deviation. Angle of horizontal and vertical deviation were 11.76 ± 6.97 PD and 9.62 ± 9.95 PD, respectively. AchR Ab was positive in 14 (38.89%) patients and abnormal RNST was found in 6 (16.67%) patients. Ice test was positive in 15 (71.43%) patients of 21 patients with ptosis. Abnormal thymic lesion (thymoma or thymic lesion) was presented in 7 (19.44%) patients and 6 (16.67%) patients had a thyroid disease. Unequivocal response to pyridostigmine was observed in 31 (86.11%) patients

Table 1
Demographics of total patients for ocular myasthenia gravis.

Parameters	
Total patients (n)	36
Male: Female (n)	18 (50.0%): 18 (50.0%)
Age at time of onset (yr)	50.39 ± 13.57 (range: 19–74)
Duration of follow-up (mo)	10.1 ± 13.3 (range: 4–26)
Ocular symptoms (n)	
Ptosis	12 (33.33%)
Diplopia	14 (38.89%)
Ptosis and Diplopia	10 (27.78%)
Ptosis grade (1:2:3) (22) (n)	9 (40.91%): 9 (40.91%): 4 (18.18%)
Horizontal deviation (24) (n)	18 (75.0%)
Vertical deviation (24) (n)	13 (54.17%)
Angle of horizontal deviation (PD)	11.76 ± 6.97
Angle of vertical deviation (PD)	9.62 ± 9.95
Seropositive AchR Ab (n)	14 (38.89%)
AchR Ab titer (nmol/L)	2.63 ± 4.26
Abnormal RNST (n)	6 (16.67%)
Positive ice test (21) (n)	15 (71.43%)
Abnormal thymic lesion (n)	7 (19.44%)
Thyroid disease (n)	6 (16.67%)
Other autoimmune disease (n)	3 (8.33%)
Response to pyridostigmine (n)	31 (86.11%)
Treatment to steroid (n)	16 (44.44%)
Side effects of treatment (n)	5 (13.89%)

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, PD = prism dioptres, RNST = repetitive nerve stimulation test, SD = standard deviation.

Table 2
Comparison characteristics between confirmed and possible ocular myasthenia gravis.

Parameters	Confirmed OMG (n = 15)	Possible OMG (n = 21)	<i>P</i> value
Age at time of onset (yr)	56.87 ± 13.36	45.76 ± 3.42	.050
Male: Female (n)	8: 7	10: 11	>.999
Ocular symptoms (n)			
Ptosis	3 (20.0%)	9 (42.86%)	.836
Diplopia	5 (33.33%)	9 (42.86%)	>.999
Ptosis and Diplopia	7 (46.67%)	3 (14.28%)	.121
Ptosis grade (1:2:3) (22) (n)	4: 3: 3	5: 6: 1	.460
Horizontal deviation (24) (n)	9 (75.0%)	9 (75.0%)	>.999
Vertical deviation (24) (n)	8 (66.67%)	5 (41.67%)	.338
Angle of horizontal deviation (PD)	13.50 ± 8.23	10.22 ± 5.67	.692
Angle of vertical deviation (PD)	7.25 ± 3.99	13.40 ± 10.49	.740
Seropositive AchR Ab (n)	14 (93.33%)	0 (0%)	<.001
Abnormal RNST (n)	6 (40.0%)	0 (0%)	.003
Positive ice test (21) (n)	8 (88.89%)	7 (58.33%)	.489
Abnormal thymic lesion (n)	7 (46.67%)	0 (0%)	.001
Thyroid disease (n)	2 (13.33%)	4 (19.05%)	>.999
Other autoimmune disease (n)	1 (6.67%)	2 (9.52%)	>.999
Treatment to steroid (n)	10 (66.67%)	6 (28.57%)	.041
Side effects of treatment (n)	1 (6.67%)	4 (19.05%)	.376

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, OMG = ocular myasthenia gravis, PD = prism dioptres, RNST = repetitive nerve stimulation test, SD = standard deviation.

and 16 (44.44%) patients were administered steroid for treatment (Table 1).

3.2. Comparison between groups with confirmed OMG vs possible OMG

Patients were divided into 2 groups according to AchR Ab and RNST results: confirmed OMG and possible OMG. Fifteen patients were in the group with confirmed OMG, consisting of 14 patients who were seropositive for AchR Ab and 1 patient who are seronegative with positive RNST. All of patients with abnormal thymic lesion (n=7) were in the confirmed OMG group. Treatment with steroid was performed more for the confirmed OMG than for the possible OMG group (*P* = .041). However, clinical presentation of ocular symptoms, ptosis grade, angle of horizontal or vertical deviation, and ice test were not significantly different (Table 2).

3.3. Comparison between groups according to ocular symptoms

Patients were divided into 2 groups according to ocular symptoms (ptosis and diplopia): both 2 clinical symptoms (n = 10) and 1 clinical symptom (n = 26). Vertical deviation was more prominent in the group with 2 clinical symptoms (90.0%) than that in the 1 clinical symptom group (28.57%) (*P* = .005). The angle of vertical deviation was also significantly higher in the group with 2 clinical symptoms (*P* = .019). For seropositive cases, AchR Ab titer was significantly higher in the group with 2 clinical symptoms than that in the 1 clinical symptom group (5.27 ± 4.89, 1.62 ± 3.60, *P* = .011). However, ptosis grade, angle of horizontal deviation, and ice test were not significantly different between the 2 groups (Table 3). We also compared the 2 clinical symptoms

Table 3
Comparison characteristics following to ocular symptoms.

Parameters	Ptosis and Diplopia (n = 10)	Ptosis or Diplopia (Ptosis = 12; Diplopia = 14)	P value
Age at time of onset (yr)	50.90 ± 12.22	52.21 ± 16.94	.427
Male: Female (n)	4: 6	14: 12	.457
Ptosis grade (1:2:3) (22) (n)	4: 3: 3	5: 6: 1	.460
Horizontal deviation (24) (n)	7 (70.0%)	11 (78.57%)	.651
Vertical deviation (24) (n)	9 (90.0%)	4 (28.57%)	.005
Angle of horizontal deviation (PD)	10.67 ± 5.57	12.36 ± 7.81	.756
Angle of vertical deviation (PD)	12.22 ± 11.07	3.75 ± 1.71	.019
Seropositive AchR Ab (n)	6 (60.0%)	8 (30.77%)	.140
AchR Ab titer (nmol/L)	5.27 ± 4.89	1.62 ± 3.60	.011
Abnormal RNST (n)	3 (30.0%)	3 (11.54%)	.317
Positive ice test (21) (n)	7 (70.0%)	8 (66.67%)	>.999
Abnormal thymic lesion (n)	4 (40.0%)	3 (11.54%)	.076
Thyroid disease (n)	2 (20.0%)	4 (15.38%)	>.999
Other autoimmune disease (n)	2 (20.0%)	1 (3.85%)	.181
Treatment to steroid (n)	6 (60.0%)	10 (38.46%)	.286
Side effects of treatment (n)	1 (10.0%)	4 (15.38%)	>.999

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, PD = prism dioptres, RNST = repetitive nerve stimulation test, SD = standard deviation.

and the group with diplopia alone (Table 4). Similar to the previous results, only vertical deviation showed a statistically significant difference.

4. Discussion

Our study presented detailed analysis of ocular symptoms in 36 OMG patients, in subjective and objective (grading of ptosis, measurement of ocular deviations) manners. Patients who had 2 clinical ocular symptoms (ptosis and diplopia) showed severe degree of each symptom, with higher AchR Ab titer ($P = .011$), than those with 1 clinical symptom (ptosis or diplopia). However, in other laboratory test results were not significantly different between the 2 groups. Those with possible OMG defined as patients who had symptoms of OMG without positive laboratory test results excluding unequivocal antimuscarinic treatment

(pyridostigmine) showed similar individual symptom severity and ice test positivity with those who had laboratory confirmed OMG. The proportion of abnormal thymic lesions, is most distinctive feature between confirmed and possible groups, all of patients with abnormal thymic lesion ($n = 7$) were in the confirmed OMG group ($P = .001$). We tried to figure out the diagnostic positivity for OMG possible patients. Among 67 patients with typical OMG symptoms underwent diagnostic tests, 15 (20.9%) patients were confirmed to be positive for AchR Ab and RNST and 21 (31.3%) patients were found to have unequivocal antimuscarinic treatment response during 4 years (2016–2020). Overall, about half of patients were highly suspicious for OMG. Although OMG/GMG patients show decremental response of AchR Ab^[10–13] to 50% to 70% and RNST^[14,15] to 19% to 33%, having suspicion and performing OMG diagnostic work for patients with typical symptoms are still helpful for ophthalmologists. OMG is called the great masquerader owing to its varied clinical presentations.^[16] Variable weakness of levator palpebrae superiors complex/extraocular muscles (EOM) is a hall mark of this disease and it is results makes truly diagnostic signs (Cogan's lid twitch, e.g.,). According the MGFA Clinical Classification, all pure OMG severity corresponded to Class I, there was no reliable evaluation index for ocular symptoms.^[17] However, reliable severity assessment is crucial for treatment response monitoring, follow-up and differential diagnosis. Not only ptosis, but also diplopia should be quantitatively measured to reflect the severity and improvement of OMG. The frequency and clinical features of MG seronegative for AchR Ab seem to show ethnic and regional differences.^[18] As widely known, seronegative OMG is much more frequent compare to overall MG and it is definitely related to the sensitivity of antibody (Ab) tests.^[9] Moreover, in some cases, the concentration of previously known Ab is too low to be detected, the symptom of OMG might be caused by an Ab against an unknown antigen, or caused by genetic variation of rapsyn or other muscle protein, not by the Ab. As reflected in various cases, clinical features can be heterogeneous.^[19] In our cases, 21 patients without laboratory positive results had OMG symptom relived with antimuscarinic treatment. We called this patient

Table 4
Comparison characteristics between 2 clinical symptoms and diplopia symptom.

Parameters	Ptosis and Diplopia (n = 10)	Diplopia (n = 14)	P value
Age at time of onset (yr)	50.90 ± 12.22	52.21 ± 16.94	.861
Male: Female (n)	4: 6	9: 5	.526
Horizontal deviation (24) (n)	7 (70.0%)	11 (78.57%)	.651
Vertical deviation (24) (n)	9 (90.0%)	4 (28.57%)	.005
Angle of horizontal deviation (PD)	10.67 ± 5.57	12.36 ± 7.81	.756
Angle of vertical deviation (PD)	12.22 ± 11.07	3.75 ± 0.85	.019
Seropositive AchR Ab (n)	6 (60.0%)	5 (35.71%)	.270
AchR Ab titer (nmol/L)	5.27 ± 4.89	1.93 ± 4.89	.074
Abnormal RNST (n)	3 (30.0%)	1 (7.14%)	.155
Abnormal thymic lesion (n)	4 (40.0%)	1 (7.14%)	.155
Thyroid disease (n)	2 (20.0%)	1 (7.14%)	.534
Other autoimmune disease (n)	2 (20.0%)	0 (0%)	.174
Treatment to steroid (n)	6 (60.0%)	5 (35.71%)	.586
Side effects of treatment (n)	1 (10.0%)	1 (7.14%)	.484

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, PD = prism dioptres, RNST = repetitive nerve stimulation, SD = standard deviation.

group as “possible OMG” and tried to figure out their distinctive features compare to OMG patients who were confirmed to be positive for AchR Ab and RNST. The individual symptom sensitivity assessment was similar between 2 groups. The ice test positivity was lower in the possible group but the difference between the 2 groups was not statistically significant. In the ice test, the positive rate is about 70% in all patients, the confirmed group is 90%, and the possible group is 60%, with the highest positive rate among all tests. As in previous reports, the ice test is a simple, specific, and relatively sensitive test for the diagnosis of myasthenic ptosis.^[5,6,20] In addition, Cogan’s lid twitch is reported to have a sensitivity of up to 75% and a specificity approaching 99% in MG with ptosis.^[21] The Cogan’s lid twitch, in which the ptotic lid briefly elevates excessively after a vertical saccade from a downgaze position. In other words, it can be seen that both the ice test and the Cogan’s lid twitch sign are clinically easy to do and are important clues for OMG diagnosis. Interestingly, all patients had normal thymus without any abnormal thymic lesion (thymus hyperplasia, thymoma) in possible OMG group. This result is a reminder that the thymic lesions are associated with positive AchR Ab. And, it might be explained by the lower antibody production process in the thymus, and the possibility of different pathogenesis of OMG. The possible group had similar or milder symptoms with normal thymus and they responded to pyridostigmine treatment well. In addition, less patients in the possible group needed more potent treatment like steroids. Some patients in this group might have other types of known Abs. A recent study evaluated 62 GMG patients with MG seronegative for the AchR Ab and found that 27.4% of patients are positive for Musk (Muscle-specific tyrosine kinase) Ab and 3.2% for LRP4 (LDL-related receptor-related protein 4) Ab.^[18] Overall, 39 of 70 (55.7%) GMG or OMG patients with MG remained triple seronegative for the Abs to AchR, Musk, and LRP4. As such, many studies on Ab tests are being conducted, but no Abs are identified in many patients.^[18] Also, these additional Ab tests are not available in most clinical setting. With pyridostigmine treatment, a significant number of patients would show relief of their symptoms without significant side effects. This study has some limitations. First, due to its retrospective nature, there could have been a selection bias towards patients who showed good compliance to antimuscarinic treatment. The sample might not be representative of the true prevalence of myasthenic ptosis and diplopia in the general clinic. We tried to make flow chart of included population (Fig. 1) to overcome this limitation. Those in the possible group were not the same as seronegative OMG patients, the ratio to total included patients was not quite different from known prevalence (58% of total OMG suspects). In addition, neostigmine test, sleep test, single fiber electromyography (EMG) were not performed for most patients and Ab results are also limited to AchR-binding Ab. As a result, there may be parts where neurophysiological investigations are insufficient, as reported from the perspective of the ophthalmologic department. Neostigmine test is one of the gold standard, diagnostic test for MG. However, it is hard to perform it for all of OMG suspects in an outpatient-based clinical office setting owing to its time-consuming, muscarinic receptor-associated side effects including bronchial spasm, blood pressure change, arrhythmia. Kim et al^[22] have reported that 7 of 26 patients show positive response after intravenous neostigmine administration, presenting the availability and safety of neostigmine test for diagnosis of OMG. With a careful and well-organized examination system, outpatient-based neostigmine test

could be one of the best diagnostic methods for OMG. We tried to do repeated measurement of marginal reflex distance, lid fatigability, deviation angle, including ice test for OMG suspects as many as possible. More detailed Ab tests for clustered AchR Ab, Musk Ab, LRP4 Ab would be needed, and these are possible only in laboratory settings for research. Lastly, the mean follow up period was only 10.1 months. Some patients in the possible OMG group might show positive Ab results with repeated tests in future follow-up. We are planning a cohort study with patients included in this study to find the final diagnosis and the conversion rates from OMG to GMG thorough more follow-up.

In conclusion, this study presents the usefulness and diagnostic validity of antimuscarinic treatment for OMG, especially seronegative OMG, with detailed symptom analysis. Although further study with more diverse tests for OMG is needed, clinicians should consider OMG as differential diagnosis for ptosis and/or diplopia, and actively perform tests for OMG and include antimuscarinic treatment.

Author contributions

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