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Ophthalmologic clinical features of ocular myasthenia gravis

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Abstract

To investigate the clinical features of ocular myasthenia gravis (OMG) in ophthalmology. A total of 28 patients with ptosis or diplopia who were followed for at least 6 months between March 2016 and February 2022 were included in this study. The clinical symptoms of the patients and test results were analyzed. According to the positivity of serologic or electrophysiologic test, these patients were divided into 2 groups (positive and negative OMG results) and according to the clinical symptoms of diplopia or ptosis for comparison. Ptosis, diplopia, and both ptosis and diplopia were present in 6 (21.43%), 14 (50.0%), and 8 (28.57%) patients, respectively. Acetylcholine receptor auto-antibody (AchR Ab) was positive in 16 (57.14%) of 28 patients and the ice test was positive in 13 (92.86%) of 14 patients with ptosis. Abnormal thymic lesions were presented in 7 (25.0%) patients, and a definite improvement in response to pyridostigmine was observed in 27 (100.0%) patients. Both ptosis and diplopia were significantly higher in the group with positive results than that in the negative results group ($P = .025$). In addition, both horizontal and vertical diplopia was significantly higher in the group with AchR Ab titer > 5.0 than that in the group with AchR Ab titer < 5.0 ($P = .041$). After excluding cranial nerve palsy, if there is ptosis and diplopia, especially vertical diplopia, the possibility of OMG should be considered.

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: angle of deviation, diplopia, ocular myasthenia gravis, ptosis, pyridostigmine

1. Introduction

Ocular myasthenia gravis (OMG) is an autoimmune disorder associated with neuromuscular junction abnormalities at the ocular muscle level. Approximately 50% to 60% of patients with myasthenia gravis (MG) initially present with ocular symptoms such as ptosis, diplopia, and ophthalmoplegia.[1] Moreover, 50% to 60% of patients presenting with OMG subsequently progress to generalized MG (GMG), commonly within the first 1 to 2 years.[2] Thus, early changes are readily detected by ophthalmologists in many patients. However, the diagnosis of OMG based on clinical findings is often challenging because OMG should be considered in the differential diagnosis of any pattern of painless, unilateral or bilateral, pupil-sparing ophthalmoplegia with or without ptosis.[3] In most patients, MG can be caused by auto-antibodies against the nicotinic acetylcholine receptor. However, such auto-antibodies were not detected in 50% of the patients with OMG, and the positivity was much lower than that with GMG (85%).[4] Other diagnostic tests including the Jolly test, ice test, rest test, and neostigmine test have varying sensitivities and specificities.[5–8] Some patients show unequivocal improvement after the antimyasthenic regimen trial, although they show no positive test findings.[8] Hence, no gold standard diagnostic test is available for MG, especially OMG. Many reports on OMG published thus far have been from the field of neurology, although most of these studies have mentioned long-term prognosis, presented as a conversion rate to GMG. Therefore, we diagnosed OMG in patients who were AchR Ab-positive or had a definite response to the antimyasthenic regimen and investigated their ophthalmologic findings in this single-center study.

2. Methods

This study was approved by the Institutional Review Board of Samsung Changwon Hospital (Changwon, Republic of Korea) and was conducted in accordance with the 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 the medical records of adult patients complaining of ptosis or diplopia with diurnal variation and fatigue between March 2016 and February 2022 at Samsung Changwon Hospital. The inclusion criteria were as follows: age 18 years or more; 6 months or more of follow-up; fulfilling our definition of OMG (the

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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presence of ptosis, diplopia or both); and at least one of the following: positive acetylcholine receptor auto-antibody (AchR Ab) test, significant response in repetitive nerve stimulation test (RNST), definite improvement in clinical response to a longer-acting acetylcholinesterase antagonist (pyridostigmine), and positive ice test. RNST was performed using the method of Oh et al[9] 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 potentialwas recorded in each tested muscle. The patients had a high clinical suspicion of OMG or were seronegative for AchR Ab; however, they were regarded as likely to have OMG clinically and responded to the diagnostic pyridostigmine treatment. There was an improvement in pyridostigmine treatment; however, some patients were administered oral steroids as needed for further treatment. AchR-binding Ab titers were analyzed using a radioactive isotope-based radioimmunoassay and titers of ≥ 0.02 nmol/L were regarded as abnormal. Exclusion criteria were: a history of active thyroid eye disease, cranial nerve palsy, 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. Demographics and clinical characteristics were obtained from medical records, including patient age at onset, sex, ocular symptoms (ptosis and/or diplopia), angle of horizontal or vertical diplopia, AchR Ab titer, ice test, presence of thymic abnormalities (i.e., thymic hyperplasia or thymoma), presence of thyroid disease, secondary GMG, pyridostigmine response, and treatment using steroids.

2.1. Ophthalmic evaluation and symptom severity assessment

At the first visit, patients underwent ophthalmologic assessment, including slit-lamp examination, measurement of horizontal/vertical deviation, and fundus photography. The horizontal and vertical deviation angles were measured using the alternating prism cover test at a distant primary position for patients with diplopia, whereas the ice test was performed for those with ptosis. In patients with diplopia, the degree of deviation was described by prism diopters (PD). The ice test was judged positive if there was an improvement in the marginal reflex distance from at least 2.0 mm after the ice test. Mild ptosis was defined as 2 mm or less, moderate ptosis as 2 to 4 mm, and severe ptosis as ≥ 4 lower than the desired upper eyelid level. The criteria for evaluation of ptosis and diplopia was based on the grade measured at the initial visit before administration of the medication.

2.2. Subgroup analysis

Subgroup analysis was performed based on the laboratory test results and the number of initial symptoms. Based on laboratory test results, participants were classified into 2 groups: OMG with positive results, patients with positive AchR Ab or RNST, and OMG those with negative results, indicating patients presenting an unequivocal clinical response to pyridostigmine without positive AchR Ab or RNST. Patients with positive AchR Ab were further divided into 2 groups based on a 5.0 nmol/L titer and compared. The participants were divided into 2 groups based on the number of symptoms: both ptosis and diplopia; and ptosis or diplopia.

2.3. Statistical analysis

An independent statistician conducted all statistical analyses using a commercially available statistical package (STATA V.14.0; Stata Corporation, College Station, TX). Demographic differences between the groups were compared using the Mann–Whitney *U* test, Fisher's exact test, and Pearson's Chi-square test. A *P* value of < .05 was considered statistically significant.

3. Results

3.1. Baseline clinical characteristics of patients with OMG

A total of 28 patients (12 males and 16 females) were included in this study, and the mean duration of follow-up was 13.1 ± 10.3 (range: 6–26) months after the initial visit. The average age at OMG onset was 55.39 ± 14.49 (range: 20–74) years. At the initial visit, ptosis, diplopia, and both ptosis and diplopia were present in 6 (21.43%), 14 (50.5%), and 8 (28.57%) patients, respectively. Of the 14 patients with ptosis, 2 presented with mild ptosis, 8 with moderate ptosis, and 4 with severe ptosis. Of the 22 patients with diplopia, 10 (45.46%) had horizontal diplopia, 5 (22.72%) had vertical diplopia, and 7 (31.82%) had horizontal and vertical diplopia. The angle of horizontal and vertical deviations was 12.29 ± 8.51 PD and 7.42 ± 7.59 PD, respectively. AchR Ab was positive in 16 (57.14%) patients, and abnormal RNST was detected in 8 (28.57%) patients. Ice test results were positive in 13 (92.86%) of the 14 patients with ptosis. Abnormal thymic lesions (thymoma or thymic hyperplasia) were present in 7 (25.0%) patients, while 6 (21.43%) patients had thyroid disease. And 2 (7.14%) patients had autoimmune disease as rheumatoid arthritis. A favorable response to pyridostigmine was observed in 27 (100.0%) patients, and 18 (64.29%) patients were administered steroids for treatment (Table 1). In 1 patient, adverse effects occurred after pyridostigmine administration, and the clinical response could not be evaluated.

3.2. Comparison between groups with positive and negative OMG result

The patients were divided into 2 groups according to AchR Ab and RNST results: OMG with positive results and OMG with negative results. Eighteen patients were in the group positive results for OMG, consisting of 16 patients who were seropositive for AchR Ab and 2 who were seronegative with positive RNST. All patients with ptosis and diplopia (n = 8) were in the OMG with positive results group (*P* = .025). In addition, all patients with abnormal thymic lesions (n = 7) were in the OMG with positive results group (*P* = .030). Moreover, the angle of horizontal deviation (14.67 ± 8.69 PD, 6.60 ± 4.98 PD; *P* = .068) was not statistically significant, but a difference was observed (Table 2).

3.3. Comparison between groups according to the scale of AchR Ab titer

The AchR Ab titer (<5.0) and AchR Ab titer (>5.0) groups were equal to 9 patients each in 18 patients with positive results. Both horizontal and vertical diplopia were significantly different in the group with AchR Ab titer > 5.0 (71.43%) than that in the AchR Ab titer group < 5.0 (12.50%) (*P* = .041). Moreover, abnormal thymic lesions were more prominent in the group with AchR Ab titer > 5.0 (66.67%) than that in the AchR Ab titer group < 5.0 (11.11%) (*P* = .050) (Table 3).

3.4. Comparison of ocular symptoms (Ptosis and diplopia vs Ptosis or diplopia) between groups

Patients were divided into 2 groups according to ocular symptoms (ptosis and diplopia): ptosis and diplopia (n = 8) and ptosis or diplopia (n = 20). Both horizontal and vertical diplopia were more prominent in the ptosis and diplopia group (75.0%) than that in the ptosis or diplopia group (7.14%) (*P* = .002). All patients with secondary GMG (n = 4) were in

Table 1

Demographics of total patients for ocular myasthenia gravis.

Parameters	
Total patients (n)	28
Male: Female (n)	12 (42.86%): 16 (57.14%)
Age at time of onset (yrs)	55.39 ± 14.49 (range: 20–74)
Duration of follow-up (mo)	13.1 ± 10.3 (range: 6–26)
Ocular symptoms (n)	
Ptosis	6 (21.43%)
Diplopia	14 (50.0%)
Ptosis & Diplopia	8 (28.57%)
Ptosis grade (1:2:3) (14) (n)	2 (14.29%): 8 (57.14%): 4 (28.57%)
Horizontal diplopia only (22) (n)	10 (45.46%)
Vertical diplopia only (22) (n)	5 (22.72%)
Horizontal & vertical diplopia (22) (n)	7 (31.82%)
Angle of horizontal diplopia (17) (PD)	12.29 ± 8.51
Angle of vertical diplopia (12) (PD)	7.42 ± 7.59
Seropositive AchR Ab (n)	16 (57.14%)
AchR Ab titer (16) (nmol/L)	6.50 ± 4.45
Abnormal RNST (n)	8 (28.57%)
Positive ice test (14) (n)	13 (92.86%)
Abnormal thymic lesion (n)	7 (25.0%)
Thyroid disease (n)	6 (21.43%)
Other autoimmune disease (n)	2 (7.14%)
Secondary GMG (n)	4 (14.29%)
Response to pyridostigmine (27) (n)	27 (100.0%)
Treatment to steroid (n)	18 (64.29%)
Side effects of treatment (n)	5 (17.86%)

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, GMG = generalized myasthenia gravis, PD = prism diopters, RNST = repetitive nerve stimulation test, SD = standard deviation.

the ptosis and diplopia group ($P = .003$). Steroid treatment was also significantly higher in the group with ptosis and diplopia than that in the ptosis or diplopia group ($P = .025$). However, ptosis grade, angle of deviation, AchR Ab titer, and ice test results were not significantly different between the 2 groups (Table 4).

4. Discussion

The definition of OMG has not been standardized by established diagnostic criteria, especially for seronegative OMG. Therefore, this study investigated ocular symptoms in patients with OMG with AchR Ab-positive or definite improvement in the clinical response to pyridostigmine (AchR Ab-negative). A total 28 patients were analyzed, and isolated diplopia (50%) in our patients with OMG was reported more frequently than in previous cohorts, between 27% and 34%.[10,11] These differences are thought to be related to race, size of the patient, analysis of patients visited the ophthalmology department, and presence or absence of GMG. Looking at the pattern of diplopia, it can be seen that horizontal diplopia is more common than vertical diplopia, so there is more affected of horizontal extraocular muscle such as other reports in OMG.[11,12] Moreover, the 57.1% AchR Ab positivity rate was similar to that in previous reports (50%–60%).[4,13]

Positive results group showed 2 more clinical ocular symptoms (both ptosis and diplopia), than the group with negative results. The type of diplopia and angle of deviation results were clinically different, but there was no statistically significant difference between the 2 groups. Since there are more cases with 2 clinical symptoms and patients with a large deviation angle for both horizontal and vertical diplopia in the positive results group, the patient might be complain of severe subjective symptoms. The proportion of abnormal thymic lesions was the most distinctive feature between the positive and negative results groups, and all patients with abnormal thymic lesions (n = 7) (38.89%) were in the positive OMG result group. In addition, abnormal thymic lesions were more prominent in the group with AchR Ab titer > 5.0 (66.67%) than that in the AchR Ab titer group < 5.0 (11.11%). In the AchR Ab-positive group, both clinical symptoms and abnormal thymic lesions were more frequent, and thymic lesions were more strongly correlated with high Ach R Ab titers. In previous reports, if there were 2 clinical symptoms (ptosis and diplopia) or an abnormal thymic lesions, poor prognosis or increased secondary GMG was reported.[14,15] Both horizontal and vertical diplopia were more prominent in the group with AchR Ab titer > 5.0 (71.43%) than that in the AchR Ab titer group < 5.0 (12.50%), as were the angle of vertical diplopia (11.40 ± 10.71 vs 4.0 ± 2.31 PD). In other words, owing to the high AchR Ab titer, severe ocular symptoms and the abnormal thymic lesions in cases, we should closely monitor the prognosis and secondary GMG. In this study, GMG conversion was observed in 14.3% of patients during the study period. Since this result is a value during the 13 months follow-up period, it is difficult to determine the GMG conversion rate. The

Table 2

Comparison characteristics between groups with positive and negative OMG result.

Parameters	Positive result (n = 18)	Negative result (n = 10)	*P* value
Age at time of onset (yrs)	57.61 ± 15.41	51.40 ± 12.38	.125
Male: Female (n)	8: 10	4: 6	>.999
Ocular symptoms (n)			
Ptosis	3 (16.67%)	3 (30.0%)	.115
Diplopia	7 (41.18%)	7 (70.0%)	.234
Ptosis & Diplopia	8 (44.44%)	0 (0.00%)	.025
Ptosis grade (1:2:3) (14) (n)	2: 6: 3	0: 2: 1	>.999
Horizontal or vertical diplopia (n)	9 (50.0%)	6 (60.0%)	.526
Horizontal & vertical diplopia (n)	6 (33.33%)	1 (10.0%)	.350
Angle of horizontal diplopia (17) (PD)	14.67 ± 8.69	6.60 ± 4.98	.068
Angle of vertical diplopia (12) (PD)	8.11 ± 8.64	5.33 ± 3.06	.923
Seropositive AchR Ab (16) (n)	16 (88.89%)	0 (0.00%)	<.001
Abnormal RNST (8) (n)	8 (44.44%)	0 (0.00%)	.025
Abnormal thymic lesion (n)	7 (38.89%)	0 (0.00%)	
Thyroid disease (n)	4 (22.22%)	2 (20.0%)	>.999
Secondary GMG (n)	4 (22.22%)	0 (0.00%)	.265
Treatment to steroid (n)	13 (72.22%)	5 (50.0%)	.240
Side effects of treatment (n)	4 (22.22%)	1 (10.0%)	.626

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, GMG = generalized myasthenia gravis, PD = prism diopters, RNST = repetitive nerve stimulation test, SD = standard deviation.

Table 3

Comparison characteristics between groups according to the scale of AchR Ab titer.

Parameters	AchR Ab titer < 5.0 (n = 9)	AchR Ab titer > 5.0 (n = 9)	*P* value
Age at time of onset (yrs)	57.0 ± 14.30	51.40 ± 12.38	.658
Male: Female (n)	4: 5	4: 5	>.999
Ptosis grade (1:2:3) (11) (n)	2: 1: 1	0: 5: 2	.179
Ocular symptoms (n)			
Ptosis	1 (11.11%)	2 (22.22%)	>.999
Diplopia	5 (55.56%)	2 (22.22%)	.437
Ptosis & Diplopia	3 (33.33%)	5 (55.56%)	.637
Horizontal or vertical diplopia (15) (n)	7 (62.50%)	2 (100.0%)	.200
Horizontal & vertical diplopia (15) (n)	1 (12.50%)	5 (71.43%)	.041
Angle of horizontal diplopia (12) (PD)	18.60 ± 10.90	11.86 ± 6.09	.320
Angle of vertical diplopia (9) (PD)	4.00 ± 2.31	11.40 ± 10.71	.123
AchR Ab titer (nmol/L)	2.02 ± 1.54	10.0 ± 1.99	<.001
Abnormal RNST (n)	4 (44.44%)	4 (44.44%)	>.999
Abnormal thymic lesion (n)	1 (11.11%)	6 (66.67%)	.050
Thyroid disease (n)	2 (22.22%)	2 (22.22%)	>.999
Secondary GMG (n)	1 (11.11%)	3 (33.33%)	.576
Treatment to steroid (n)	5 (55.56%)	8 (88.89%)	.294
Side effects of treatment (n)	3 (33.33%)	1 (11.11%)	.576

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, GMG = generalized myasthenia gravis, PD = prism diopters, RNST = repetitive nerve stimulation test, SD = standard deviation.

Table 4

Comparison characteristics of ocular symptoms (ptosis and diplopia vs ptosis or diplopia).

Parameters	Ptosis and Diplopia (n = 8)	Ptosis or Diplopia (ptosis = 14; diplopia = 6)	*P* value
Age at time of onset (yrs)	51.75 ± 18.68	56.85 ± 12.72	.558
Male: Female (n)	2: 6	10: 10	.401
Ptosis grade (1:2:3) (n)	1: 5: 2	1: 3: 2	>.999
Horizontal & vertical diplopia (n)	6 (75.0%)	1 (7.14%)	.002
Angle of horizontal diplopia (17) (PD)	12.67 ± 5.43	12.09 ± 10.05	.609
Angle of vertical diplopia (12) (PD)	8.88 ± 8.90	4.50 ± 3.00	.375
Seropositive AchR Ab (n)	7 (87.50%)	9 (45.0%)	.088
AchR Ab titer (7 vs 9) (nmol/L)	7.61 ± 3.29	5.64 ± 5.20	.427
Abnormal RNST (n)	4 (50.0%)	4 (20.0%)	.172
Abnormal thymic lesion (n)	3 (37.50%)	4 (20.0%)	.371
Thyroid disease (n)	3 (37.50%)	3 (15.0%)	.311
Secondary GMG (n)	4 (50.0%)	0 (0.00%)	.003
Treatment to steroid (n)	8 (100.0%)	10 (50.0%)	.025
Side effects of treatment (n)	2 (25.0%)	3 (15.0%)	.606

Values are presented as mean ± SD.

AchR Ab = acetylcholine receptor auto-antibodies, GMG = generalized myasthenia gravis, PD = prism diopters, RNST = repetitive nerve stimulation test, SD = standard deviation.

reported rate of conversion to GMG is variable in earlier studies between 20.9% and 55%, possibly due to different durations of follow-up periods, different inclusion criteria, and possible effect of immunosuppressive treatment.[2,10,11,15]

Interestingly, all patients had normal thymus without any abnormal thymic lesions (thymus hyperplasia, thymoma) in the negative result OMG group. This result suggests that thymic lesions are associated with a positive AchR Ab. The negative result group had milder symptoms with a normal thymus and responded well to pyridostigmine treatment. Some patients in this group might have had other types of Abs. A recent study evaluated 62 GMG patients who were MG seronegative for AchR Ab and found that 27.4% of patients were positive for Musk (Muscle-specific tyrosine kinase) Ab and 3.2% for LRP4 (LDL-related receptor-related protein 4) Ab.[16] In other report,[17] Musk Ab was positive at 14.6% and LRP4 Ab was 16.4%, suggesting that the positive rate was variously reported. Many studies on Ab tests are being conducted, but no Abs have been identified in many patients. In addition, these Ab tests are not available in most clinical settings.

Comparison according to ophthalmologic clinical symptoms in this study showed that the group with both ptosis and diplopia had both horizontal and vertical diplopia, GMG conversion, and cases requiring steroid treatment than the group with ptosis or diplopia. All 8 patients with ptosis and diplopia also had vertical diplopia and were treated using steroids. In these results, if there is ptosis and diplopia, and it is accompanied by vertical diplopia, OMG may be considered preferentially unless it is a finding suitable for cranial nerve palsy, thyroid ophthalmopathy, Miller-Fisher syndrome, chronic progressive external ophthalmoplegia, or other neuromuscular junction disorders.[18] Additionally, if the clinical symptoms of ptosis and diplopia exist, the administration of immunosuppressants such as steroids should be considered after the acetylcholinesterase antagonist, and the possibility of conversion to GMG is high. Low and moderate dose corticosteroids have been shown to improve diplopia in OMG, and some anecdotal evidence support the use of steroids to reduce the frequency of deterioration of GMG. The long-term side effects of corticosteroids may limit their use in patient with chronic MG.[19] Epidemiologic historical studies have demonstrated that the progression of OMG to GMG was 60% before the use of immunosuppressants, compared with 30% after the introduction of immunosuppressant therapy.[20]

This study has some limitations. First, owing to its retrospective single-hospital-based study, suggesting a possible selection bias. And small sample size might not represent the true prevalence of myasthenic ptosis and diplopia in general clinics. Second, the other variable tests were not performed for most patients, and Ab results were also limited to AchR-binding Ab. As a result, neurophysiologic investigations may be insufficient, as reported from the perspective of ophthalmologic department. Third, as the mean follow-up period was 13.1 months, it was not possible to investigate long-term changes in clinical features and prognosis for > 2 years. We plan to conduct a cohort study with patients included in this study to determine the final diagnosis and conversion rates from OMG to GMG thorough further follow-up.

The strength of this study is the clinical data on ocular symptoms provided by neuro-ophthalmologist in a standardized pattern and information on clinical examination from a single institution. In conclusion, after excluding of cranial nerve palsy, if there is ptosis and diplopia, especially vertical diplopia, the possibility of OMG should be considered. In addition, it is helpful the diagnosis and treatment of OMG through antimyasthenic treatment. The high AchR Ab titer, severe ocular symptoms, and abnormal thymic lesions in these cases might lead to poor prognosis and secondary GMG.

Author contributions

The conception or design of the work (Do-Hyung Kim, Shin Yeop Oh); analysis and interpretation (Hyeon Cheol Roh, Shin Yeop Oh); data collection and drafting the work (Do-Hyung Kim, Shin Yeop Oh); critical revision of the article (Do-Hyung Kim, Hyeon Cheol Roh, Shin Yeop Oh); final approval of the version (Shin Yeop Oh).

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