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Ocular manifestation and generalization after ocular onset in ocular myasthenia gravis: A 5-year analysis

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Abstract

Background: Ocular Myasthenia Gravis (OMG) is an autoimmune disease which causes ptosis, diplopia, or both. There is very limited information on the presenting symptoms, treatment trends, factors influencing generalization, and treatment outcome in Thai populations.

Objective: To investigate characteristics of the presenting symptoms, associated factors for conversion to Generalized-MG (GMG), and treatment outcome in OMG patients.

Methods: We analyzed data from patients diagnosed with OMG between January 2015 and December 2020 at Rajavithi Hospital, Thailand. We investigated disease generalization in time-to-event analysis and compared factors associated with disease generalization using a Cox-proportional-hazards model.

Results: Of the 155 consecutive patients, 106 (68.4%) were female and their mean (SD) age was 49.3 years (15.51). There were 123 (79.35%) and 32 (20.6%) patients in the remained OMG and GMG groups respectively. Ptosis was the presenting symptom in 147 (94.8%) patients, diplopia alone was found in 8 (5.2%), and both symptoms were present in 53 (34.2%) patients. GMG patients had a higher proportion of combined ptosis and diplopia (p = 0.01), and positive AChR-Antibody test (p = 0.013). Overall, 32 (20.65%) patients converted to GMG, mostly in the first 48 months. Multivariate Cox-proportional-hazard model identified positive AChR-Ab test as a risk factor for generalization (HR, 5.32, 95% CI; 1.02-27.84).

Conclusions: The conversion rate to GMG in our study was 20.65%. The presence of AChR-Ab was identified as a risk factor for generalization of the disease; therefore, patients with OMG should be advised to test for AChR-Ab for both diagnosis and prognosis purpose.

Key word: Ocular Myasthenia Gravis; Generalized Myasthenia Gravis; Ptosis; Diplopia; Autoantibodies/immunology; Receptors, Cholinergic/immunology; AChR antibodies; Acetylcholinesterase inhibitors; Treatment outcome

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Introduction

Ocular myasthenia gravis (OMG) is an autoimmune disease that targets acetylcholine receptors at the neuromuscular junction (NMJ), resulting in weakness in the extraocular muscles and the levator palpebrae superioris. It is one of the most common neuromuscular junction diseases,[1] and its presenting symptoms include ptosis and diplopia, either alone or in combination.[2] Its prevalence in Thailand is 2.17 per 100,000 people.[3] Most patients with MG initially present with ocular symptoms, after which some of them will progress to secondary generalized MG. Approximately 30% of patients initially presenting with ocular symptoms of OMG develop generalized myasthenia gravis (GMG) within 2 years.[4] There is evidence from multiple studies to suspect some risk factors for generalization to GMG, such as late-onset (age at onset ≥ 50 years),[5,6] female gender,[6,7] thymoma,[7,8] and positive AChR-Ab;[5,6,9,10] however, some factors are still being debated, especially the initial manifestations.[6,11] There have also been some trials that have investigated the early use of immunosuppressants to prevent generalization to GMG.[5,7,12]

The purposes of this study at Rajavithi Hospital were to describe the characteristics of the presenting ocular manifestations of OMG, to investigate outcome of treatment in terms of generalization to GMG, and to evaluate factors associated with generalization.

Methods

Study design and overview

We conducted a retrospective chart review of patients diagnosed with OMG between January 2015 and December 2020. The study was approved by Rajavithi Hospital Research Ethics Committee. We reviewed diagnosis of OMG in the electronic medical records, and all patients were recruited from the database of the Ophthalmic and Neurology Outpatient Department of Rajavithi Hospital during that time period. Patients were eligible for inclusion if they were aged 18 or older and fulfilled the diagnosis criteria of OMG in accordance with Osserman and Genkins as follows: had extraocular muscle involvement with diplopia, ptosis, or both, with at least 1 of the following confirmatory tests:[13]

(1) positive acetylcholine receptor antibody (AChR Ab) titer;
(2) positive result of single fiber electromyography test;
(3) clinical response to edrophonium (Tensilon test);
(4) positive result of Repetitive Nerve Stimulation (RNS) test.

The exclusion criteria included history of prior lid or strabismus surgery, GMG occurrence at the onset of symptoms, follow-up time less than 4 months or follow-up visits < 2 times, special conditions such as pregnancy, malignancy, HIV infection; or incomplete medical records. Diagnosis of GMG was performed by neurologists based on the signs and symptoms of generalization (e.g., difficulty in swallowing, impaired speech and chewing, limited facial expression, proximal muscle weakness, and respiratory failure).

Data collection

Demographic and clinical data were obtained from medical records. Baseline characteristics were recorded including gender; age at onset; initial ocular symptoms at disease onset, including ptosis, diplopia, or both; coexisting thyroid disorders or autoimmune diseases; and presence of thymic abnormalities diagnosed by contrast computed tomography (CT). Data from laboratory results including serum acetylcholine receptor autoantibodies (AChR-Ab) were also collected. We recorded dates of OMG diagnosis, first therapy, treatments received prior to conversion to GMG (e.g., acetylcholinesterase inhibitors, immunosuppressive agents including corticosteroids; azathioprine or both, thymectomy) and time to GMG conversion in months.

Statistical analysis

Continuous variables were expressed as mean (SD), outcomes between groups were compared using T-test and categorical variables were expressed in percentages and were compared with the chi-squared test. Survival analysis was performed on 134 patients who had a follow-up time of more than 4 months. The Cox-proportional-hazard model was employed for univariate and multivariate analysis to obtain the hazard ratios (HRs) for risk factors of generalization to GMG at 5-year follow-up. The generalization to OMG was estimated using Kaplan-Meier analysis. This was adjusted for the baseline values that influenced generalization to GMG, as well as for those considered relevant based on the literature as follows: (1) Gender. GMG is more common in women, according to a previous study,[7] and it is well known that females are associated with more severe autoimmune diseases, which is attributable to the estrogen mechanism that stimulates immune response;[14] (2) Age of onset, although there is conflicting evidence as to whether or not is a risk factor;[4,6] however, older age is associated with more comorbidities and greater prevalence of thymoma[15] and may be a risk factor for the disease; (3) Combined symptoms of ptosis and diplopia at disease onset, as this factor has been considered as a surrogate of more severe disease;[16] (4) Immunosuppressive treatments;[5,7,12] and (5) History of thymoma, as there is conflicting data on whether thymectomy is beneficial in OMG patients.[17,18]

Potential risk factors identified by univariate analyses with a p-value of less than 0.2 were included in the multivariate analyses, and a p-value less than 0.05 was considered statistically significant. Analyses were performed with SPSS ver. 25 (SPSS Inc., Chicago, IL, USA).

Results

A total of 203 patients with OMG were initially included in our cohort. We excluded 48 patients in accordance with our exclusion criteria as follows: 33 patients had a follow-up time less than 4 months or follow-up visits < 2 times, 7 patients were diagnosed with GMG, 5 were pregnant, 2 patients had malignancy, and 1 had HIV infection. A total of 155 patients with OMG who fulfilled our inclusion criteria were identified from our retrospective chart review: 33 had positive AChR-Ab; 22 (out of 30 tested) had a positive result for single fiber electromyography; 21 (out of 37 tested) had positive results for repetitive nerve stimulation (RNS) test; 26 patients had a clinical response to edrophonium (Tensilon test positive); and 53 had a response to acetylcholinesterase inhibitor (AChEi). **Table 1** summarizes participants' demographic data and related clinical characteristics. Mean age (SD) of all patients was 49.3 (15.51) years, the mean (SD) age was equal in both groups (49.98 [15.09] years in OMG vs. 46.69 [17.02] years in GMG, respectively). With regard to age of onset, 77 (49.7%) and 78 (50.3%) patients were in the early onset (< 50 years) and late-onset groups respectively. Female gender was more common in both groups (65.9% in OMG and 78.1% in GMG, respectively). As the initial ocular manifestation, almost all patients were present with ptosis (n = 147, 94.8%), while 8 (5.2%) patients presented with diplopia alone and one-third (34.2%) had both ptosis and diplopia. There was a significant difference in presenting symptoms between OMG and GMG group in combined symptoms at disease onset. (p = 0.01)

Table 1. Baseline characteristics of OMG patients at initial diagnosis.

Clinical characteristics No., (%)	Total	Secondary generalization		*p* value
	(N = 155)	OMG (n = 123)	GMG (n = 32)	
Age – yrs (SD)	49.3 (15.51)	49.98 (15.09)	46.69 (17.02)	0.29
Age of onset†				0.103
Early-onset	77 (49.7)	57 (46.3)	20 (62.5)	
Late-onset	78 (50.3)	66 (53.7)	12 (37.5)	
Gender (female)	106 (68.4)	81 (65.9)	25 (78.1)	0.184
Ocular manifestations				
Ptosis	147 (94.8)	117 (95.1)	30 (93.8)	0.76
Right	41 (27.9)	32 (27.35)	9 (30)	
Left	38 (25.9)	34 (29)	4 (13.3)	
Bilateral	68 (46.2)	51 (43.5)	17 (56.6)	
Isolated Diplopia‡	8 (5.2)	6 (4.9)	2 (6.3)	0.669
Ptosis and diplopia	53 (34.2)	36 (29.3)	17 (53.1)	0.01*
AChR antibody n = 59., (%)				0.013*
Positive	33 (55.9)	21 (46.7)	12 (85.7)	
Presence of thymic abnormalities	30 (19.4)	20 (16.3)	10 (31.3)	0.056
Presence of other autoimmune disorders	14 (9.2)	11 (9.1)	3 (9.4)	0.96

†Early-onset MG: age at onset < 50 years, Late-onset MG: age at onset ≥ 50 years.
‡The presence of isolated diplopia at disease onset.
AChR denotes acetylcholine receptor.

Table 2. Ocular manifestations in OMG patients.

No., (%)	Total	Age of onset		*p* value
	(N = 155)	Early-onset (n = 77)	Late-onset (n = 78)	
Ptosis	147 (94.8)	70 (90.9)	77 (98.7)	0.034*
Right	41 (27.9)	19 (27.1)	22 (28.6)	
Left	38 (25.8)	22 (31.4)	16 (20.8)	
Bilateral	68 (46.2)	29 (41.4)	39 (50.6)	
Isolated Diplopia†	8 (5.2)	7 (9.1)	1 (1.3)	0.034*
Ptosis and diplopia	53 (34.2)	26 (33.8)	27 (34.6)	0.911

†The presence of isolated diplopia at disease onset.

Table 3. Treatment modalities in OMG patients.

No., (%)	Total	Secondary generalization		*p* value
	(N = 155)	OMG (n = 123)	GMG (n = 32)	
Treatments	139 (89.7)	113 (91.9)	26 (81.3)	0.079
Cholinesterase inhibitors	137 (98.7)	111 (98.2)	26 (100)	0.157
Cholinesterase inhibitors plus immunosuppressive	74 (53.2)	65 (57.5)	9 (34.6)	0.013*
Immunosuppressive†	83 (60)	74 (65.5)	9 (34.6)	0.001*
Corticosteroids	65 (46.8)	59 (52.2)	6 (23.1)	0.003*
Corticosteroids with azathioprine	16 (11.5)	13 (11.5)	3 (11.5)	1.000
Azathioprine	2 (1.4)	2 (1.8)	0 (0)	1.000
No medication	16 (10.3)	10 (8.1)	6 (18.8)	
Thymectomy	15 (9.7)	9 (7.3)	6 (18.8)	0.051

†Immunosuppressive therapy, corticosteroids or azathioprine or combined corticosteroids with azathioprine.

Among the 59 patients who were evaluated for AChR-Ab, 33 (55.9%) were positive. there was a high predominance of seropositive patients in the GMG group, (85.7% vs. 46.7%, $p = 0.013$). Thymoma was radiologically diagnosed and was detected in 30 (19.4%) patients, and thymectomy was performed in 15 (50%) cases. Although thymoma was more common in the GMG group, there was no statistically significant difference between the two groups ($p = 0.056$). The presence of associated autoimmune diseases, of which thyroid disorders were the most frequently found, was observed in 14 patients, and the most common of these was Graves' disease (6 patients). (**Table S1** in the Supplementary Appendix). There were 3 and 2 cases of Hashimoto's disease and Systemic Lupus Erythematosus respectively, and there was one case each of rheumatoid arthritis, optic neuritis and autoimmune hemolytic anemia.

The patients were prescribed various treatments as follows (**Table 3**): 137 (98.7%) had symptomatic treatment, receiving only AChEi; 74 (53.2%) patients receiving AChEi and immunosuppressive agents. Immunosuppressive treatments (corticosteroids or azathioprine or combined corticosteroids with azathioprine) were prescribed for 83 (60%) patients; corticosteroids alone were taken by 65 (46.8%) with mean dose of oral prednisolone 17 mg/day; corticosteroids with azathioprine were taken by 16 (11.5%); azathioprine alone was taken by 2 (1.4%). There was a significant difference in the number of patients receiving immunosuppressive agents, corticosteroids in the remained OMG and GMG groups ($p = 0.001$, $p = 0.003$ respectively) however no significant difference in patients receiving corticosteroids with azathioprine or azathioprine alone. There were 16 (10.3%) patients received no medication as they had complete stable remission during the observation period.

Among 155 patients included, 134 had a follow-up time of ≥ 4 months and were included in the time-to-event analyses. The univariate and multivariate analyses were performed using a Cox-proportional-hazards regression model (**Table 4**). Univariate analysis showed that the statistically significant hazards ratio of generalization were combination of ptosis and diplopia at onset (HR, 2.21, 95% CI; 1.09–4.49; $p = 0.027$), and positive AChR-Ab test (HR, 7.01, 95% CI; 1.48–33.10; $p = 0.014$). Receiving corticosteroids lowered the hazard of generalization, with univariate hazard ratio 0.27 (95% CI, 0.11–0.65; $p = 0.001$). The presence of associated autoimmune diseases was excluded because of the small number of OMG patients in this cohort with this category of coexisting diseases. After the final multivariate analysis was performed, the statistically significant factor was positive test of AChR-Ab (HR, 5.32, 95% CI; 1.02–27.84; $p = 0.048$). There was no significance in gender or age of onset in either univariate or multivariate regression analysis.

Table 4 Cox-proportional-hazards regression model analysis for secondary generalization.†

Univariate analysis variables	HR (95% CI)	*p* value
Age of onset (≥ 50 years)	0.62 (0.30–1.28)	0.196
Gender (female)	1.56 (0.67–3.62)	0.305
Ptosis and diplopia at onset	2.21 (1.09–4.49)	0.027*
Positive AChR antibody	7.01 (1.48–33.10)	0.014*
History of Thymoma	1.28 (0.58–2.78)	0.542
Presence of other autoimmune diseases	0.54 (0.13–2.27)	0.403
Corticosteroids	0.27 (0.11–0.65)	0.001
Multivariate analysis variables	**HR (95% CI)**	***p* value**
Age of onset (≥ 50 years)	0.48 (0.11–1.98)	0.307
Ptosis and diplopia at onset	2.39 (0.64–8.93)	0.194
Positive AChR antibody	5.32 (1.02–27.84)	0.048*
Corticosteroids	0.93 (0.22–3.89)	0.916

†Data were analyzed for 134 patients with the follow-up time of ≥ 4 months.

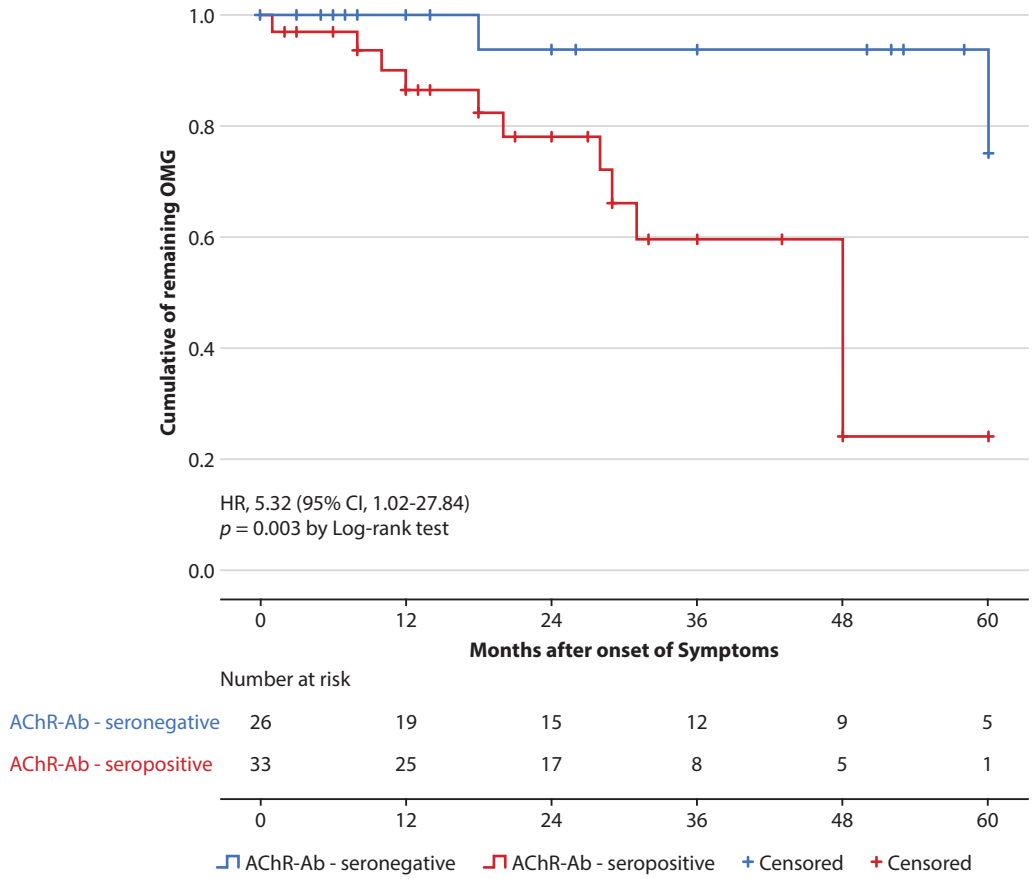

Figure 1. Kaplan-Meier curve for the cumulative remaining OMG after disease onset in seropositive and – seronegative AChR-Ab patients.

Kaplan–Meier and log-rank test indicated a significant difference in the rate of generalization in patients with positive AChR-Ab compared with those with seronegative AChR-Ab (p = 0.003, **Figure 1**). Of the 155 patients with OMG, 32 (20.6%) converted to GMG. Among these, 8 (25%) patients did so within the first 1 year, another 12 (37.5%; cumulative, 62.5%) during the second year. and the remaining 12 (37.5%) converted after 2 years from symptom onset.

Discussion

Our series was a retrospective study of conversion rates and associated factors that predict generalization to GMG. In our study, the conversion rate was 20.6% with an average time to conversion of 47.75 months from initial diagnosis of GMG. The conversion rate was higher in seropositive AChR-Ab patients within the 5 years of follow-up time. The presence of AChR-Ab was found to be a significant predictor of generalization in both univariate and multivariate Cox-proportional-hazard models. Our results were consistent with those of previous studies which demonstrated the positive correlation of AChR-Ab titer level with the severity of MG[19] and highlighted seropositivity as a risk factor of having conversion.[5,6,9,10,20]

Demographic factors such as age of onset and gender were not found to be significant in predicting generalization in either univariate or multivariate models; however, we found a trend towards higher female predominance as well as slightly older age in the remained OMG group. This finding was similar to another study in Thailand;[7] conversely, several previous studies showed a higher male prevalence of OMG patients in a western country.[4,5]

The significance of ocular symptoms at onset in predicting generalization is still debated. Wang, L. et al,[16] found that ptosis and diplopia, alone or in combination, can predict generalization; in contrast, a study of Mazzoli, M. et al showed no correlation between those symptoms and predicting generalization.[6] Univariate Cox-proportional-hazard model in our series showed that having both symptoms at onset was a significant factor in predicting generalization; however, after adjustment for all associated factors, no significance was uncovered to show that it predicted generalization.

Thymoma was considered to be a risk factor of GMG in previous studies,[7,8] but other research showed no association.[4,9] Our results presented borderline significance (p = 0.056), and no difference was found in regression analysis. Since this disease is very rare in Asian population,[21] a multicenter study may be needed to determine the overall impact and to obtain accurate epidemiological data in Thailand.

Corticosteroids have shown benefits in terms of preventing generalization in some research,[5,7,12] whereas other studies have disagreed.[4,9] Interestingly, our study displayed their advantage of decreasing conversion in a univariate model (p = 0.001); however, after taking into account adjustment factors, no significant difference was found (p = 0.916).

We had some hypotheses to explain this. First, there was a delay in treatment, since our physicians preferred to prescribe corticosteroids and/or azathioprine in OMG patients with uncontrolled symptomatic treatment, so that the median time to receiving immunosuppressants was 7.2 months after ocular onset. Second, the mean dosage of azathioprine was approximately 1 mg/kg/day which was lower than the recommended dose of 2.5 mg/kg/day in a study by Palace et al.[22] Based on these reasons, there was a diluted preventive benefit, resulting in no significance in the Cox-proportional-hazard model.

The conversion rate to GMG in our study was 20.6%. This unsurprisingly high proportion could be the result of a number of factors. Firstly, OMG patients can convert to GMG at any stage of the disease, and it can be inferred from this that the mean follow-up duration in our series was sufficient to reflect the natural course of the disease. Secondly, we did not explore anti-MuSK positive OMG because this test has not yet become commercially available in Thailand, and it is possible that undetected seropositive-MuSK OMG patients might have affected the prognosis,[23] although it appears to have a low incidence in Asians,[24] and we propose that further studies should be conducted to account for this factor. Thirdly, there was only a tiny previous preventive therapeutic effect included in our cohort.

The advantages of our study included its relatively large number of patients (155, which constitutes the largest cohort examined in Thailand), as well as the fact that our OMG patients were diagnosed by experienced ophthalmologists and neurologists in our center, enabling us to have confidence in the diagnosis of OMG and rule out other cranial nerve palsy or neuromuscular diseases. Finally, this was a retrospective study, with the irremediable drawback of missing data; however, our study illustrated that abnormality of AChR-Ab was a predictor of generalization in an Asian population.

Conclusions

The conversion rate to GMG in our study was 20.6%. As the presence of AChR-Ab was identified as a risk factor for generalization of the disease, patients with OMG should be advised to test for AChR-Ab for both diagnosis and prognosis purposes.

Declarations of interest

none

Acknowledgments

The authors declare no conflicts of interest. Parinee Kemchoknatee is currently a lecturer in Ophthalmology at Rajavithi Hospital, Rangsit University. She participated as an author in the 70th anniversary textbook of medical service departments in Thailand, writing about common pitfalls in diagnosing ptosis in Neuro-oph patients. The authors would like to thank all the subjects in this study, as well as the staff at the Ethics Committee and Research Center of Rajavithi Hospital for facilitating this study.

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Table S1. Associated autoimmune diseases. (Supplements table)

No., (%)	Total	Age of onset	
	(N = 155)	Early-onset (n = 77)	Late-onset (n = 78)
Presence of other autoimmune disorders	14 (9)	12 (15.6)	2 (2.6)
Graves' disease	6	5	1
Hashimoto's disease	3	2	1
SLE	2	2	-
Rheumatoid arthritis	1	1	-
Optic neuritis	1	1	-
AIHA	1	1	-

SLE denotes Systemic Lupus Erythematosus, AIHA denotes Autoimmune Hemolytic Anemia.