

Prognostic factors for conversion to generalization in ocular myasthenia gravis

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Abstract

Patients with ocular myasthenia gravis (OMG) are frequently treated to prevent the development of generalized myasthenia gravis (GMG). This retrospective cohort study aimed to assess prognostic factors associated with conversion to GMG.

We analyzed the time from the onset of OMG symptoms to GMG in relation to demographic variables, clinical findings, initial investigation results, and treatment regimens using Kaplan–Meier survival curves and multivariate Cox proportional regression analysis.

Of 115 patients diagnosed with OMG (median follow-up time, 2.9 years), 28 (30.4%) developed GMG. The 2-year probability of GMG conversion was 23.7%. Patients with thymic abnormalities and a positive response to repetitive facial nerve stimulation had a significantly higher risk than those with negative results (hazard ratios [HR] 4.28, $P < .001$ and HR 3.84, $P = .04$, respectively). Treatment with immunosuppressants was found to be a preventive factor for secondary generalization (HR 0.36, $P = .02$).

Patients with OMG had a low risk of developing GMG. Immunosuppressive treatments may mitigate disease progression. Chest imaging and repetitive nerve stimulation should be routinely performed to assess the risk of generalization.

Abbreviations: AChEI = acetylcholinesterase inhibitor, AChR Ab = acetylcholine receptor antibodies, aHR = adjusted hazard ratio, ANA = antinuclear factor, CI = confidence interval, EOM = extraocular movement, GMG = generalized myasthenia gravis, HR = hazard ratio, IMS = immunosuppressants, IQR = interquartile range, OMG = ocular myasthenia gravis, RNS = repetitive nerve stimulation, SFEMG = single-fiber electromyography.

Keywords: generalized myasthenia gravis, immunosuppressants, ocular myasthenia gravis, repetitive nerve stimulation, thymoma

1. Introduction

Myasthenia gravis is an autoimmune postsynaptic neuromuscular transmission disorder that manifests as fatigable weakness.^[1,2] Up to 85% of patients with myasthenia gravis have ocular symptoms as an initial manifestation, and ocular myasthenia gravis (OMG) is diagnosed when a patient presents with ptosis or diplopia resulting from weakness of the orbicularis oculi or extraocular muscles.^[3,4] When the symptoms involve

other muscle groups, it is called generalized myasthenia gravis (GMG).

Patients with OMG are frequently treated with acetylcholinesterase inhibitor (AChEI) and immunosuppressants (IMS) such as corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporin.^[1,5,6] Several studies have reported that both AChEI and IMS treatment resulted in similar significant symptomatic improvement in 40% to 85% of patients.^[3–7] Other studies have found that the rate of conversion to GMG was lower in patients treated with IMS than in untreated patients, with 34% to 86% of untreated patients having secondary generalization within 2 years of onset, whereas only 6% to 17% of patients treated with IMS progressed to GMG.^[2,8–11]

Previous reports have identified various prognostic factors associated with GMG including age at onset <50 years, smoking, thymus abnormalities, positive repetitive nerve stimulation (RNS), and positive acetylcholine receptor antibodies (AChR Ab).^[10,12–19] Another recent report found the overall conversion rate was as low as 11%.^[18] The average conversion rate among people living in certain Asian countries has been reported to be 23.6%,^[13,18,19] which is lower than the mean conversion rate reported in people of European ethnicity (49.2%).^[14–17,20,21] These varying results have led to some controversy concerning the conversion rate in relation to prognosis and regarding the risks and benefits of early IMS treatment to prevent generalization in patients with OMG.

This study aimed to examine the possible prognostic factors influencing the conversion rate of OMG to GMG and determine appropriate treatment regimens to reduce conversion to generalization. The findings of this study may provide an effective treatment to improve the quality of life in patients with ocular myasthenia.

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2. Methods

Between January 2006 and April 2018, we conducted a retrospective cohort study, in which at least 2 neuro-ophthalmologists or neurologists at the Eye Clinic or Neurology Center in Songklanagarind Hospital, the primary tertiary care center in southern Thailand, reviewed the electronic medical records of patients diagnosed with OMG. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand. The Ethics Committee waived the requirement for written patient informed consent as this research posed less than minimal risk to patients and because the rights and welfare of the patients would not be adversely affected by this study. All patients manifested isolated ocular symptoms such as ptosis or diplopia, at the initial presentation <2 years prior to a diagnosis of OMG and had a confirmed final diagnosis of OMG based on one of the following tests:

1. a pharmacological test (pyridostigmine or neostigmine),
2. RNS,
3. a serum AChR Ab test, where available, and
4. an ice pack test or fatigue-induced ptosis test with a clinical response to treatment.

An ice pack test was deemed positive if there was >2 mm of improved ptosis or $\geq 50\%$ reduction in the ocular deviation with a Hess screen test after an ice pack was applied on both eyelids for 2 minutes and 5 minutes, respectively. A response to a fatigue-induced ptosis test was considered positive when a patient experienced fatigable ptosis after a sustained upgaze for 1 minute. All patients with OMG were monitored until conversion to GMG or to the last follow-up visit. We excluded patients diagnosed with congenital, infantile, or juvenile OMG. We also excluded patients who presented with systemic symptoms within 1 month of the time of diagnosis. Patients with other active eye diseases potentially mimicking OMG, such as thyroid-associated ophthalmopathy, and patients with any previous eyelid or strabismic surgeries were excluded.

We assessed the conversion rate to GMG during the follow-up visits. Patients who developed symptoms or clinical findings including axial or limb weakness, facial weakness (except in the ocular muscles), or bulbar symptoms (difficulty breathing,

swallowing, hoarseness) were defined as secondary generalizations and were diagnosed by a neurologist. Clinical examination included ocular symptoms, duration of symptoms, and eye movement assessment. Chest imaging or contrast computed tomography for detecting the anterior mediastinal lesion, antinuclear factor (ANA), a thyroid function test, electromyography studies (RNS), and tests to assess the presence of autoimmune diseases, were also undertaken. Thymus abnormalities were assessed through a positive radiological or pathological confirmation after thymectomy. RNS test was performed by an electromyographer, and muscle testing including facial and limb muscles were selected based on clinical weakness. A positive repetitive facial nerve stimulation test result was defined as >10% of a decremental response in the nasalis or orbicularis oculi muscle, which has the advantage of a diagnostic yield of OMG.^[22,23] A positive ANA was deemed as an ANA titer of 1:80 or more, detected using immunofluorescence assay. Abnormal thyroid function was diagnosed as hyperthyroidism or hypothyroidism. After a positive diagnosis of OMG, patient treatments were categorized into 2 groups, namely, IMS (corticosteroid, azathioprine, or other IMS) and non-IMS (AChEI or no medications) groups. Additionally, we recorded the time from symptom onset to the date of diagnosis, initial treatment, GMG conversion, or the last follow-up visit.

For statistical analysis, comparisons of clinical characteristics between the IMS and non-IMS treatment groups were undertaken using chi-square or Fisher exact tests for categorical variables and a Student *t* test for numeric data. The time from onset of OMG symptoms to GMG was analyzed in relation to demographic variables, clinical manifestations, investigation results, and treatment regimens using Kaplan–Meier survival curves. Variables with a *P* value <.2 from a log rank test were then included in a multivariate Cox proportional regression analysis. All data analyses were performed using R (R Core Team 2019).

3. Results

In total, we reviewed 115 patients who had been diagnosed with OMG (median follow-up time, 2.9 years; interquartile range [IQR], 1.5–5.5 years). Patients' clinical characteristics are

Table 1

Clinical characteristics of the study patients.

Variable	Total (n = 115)	No IMS (n = 34)	IMS (n = 81)	<i>P</i> value
Age at onset				.38
≤50 yr	63 (54.8)	16 (47.1)	47 (58)	
>50 yr	52 (45.2)	18 (52.9)	34 (42)	
Gender				1
Male	32 (27.8)	9 (26.5)	23 (28.4)	
Female	83 (72.2)	25 (73.5)	58 (71.6)	
Ocular symptoms				.03
Ptosis	56 (48.7)	23 (67.6)	33 (40.7)	
Diplopia	6 (5.2)	1 (2.9)	5 (6.2)	
Both	53 (46.1)	10 (29.4)	43 (53.1)	
Duration of symptoms (months)	2.1 (1–6.1)	2.7 (1,4.5)	1.9 (1,6.2)	.52
EOM limitation	46 (40)	11 (32.4)	35 (43.2)	.38
Thymus abnormalities	23/96 (24)	9/28 (32.1)	14/68 (20.6)	.48
Positive RNS	20/32 (62.5)	8/12 (66.6)	12/20 (60)	.47
Positive ANA	9/48 (18.8)	5/16 (31.3)	4/32 (12.5)	.20
Abnormal TFT	12/84 (14.3)	5/28 (17.9)	7/56 (12.5)	.27

Data are presented as n (%) or median (interquartile range).

ANA = antinuclear factor, EOM = extraocular movement, IMS = immunosuppressants, RNS = repetitive nerve stimulation, TFT = thyroid function test.

summarized in Table 1. More than two-thirds of the participants were female, and most were middle-aged (47.5 ± 14.2 years). Almost 50% presented with both ptosis and diplopia and had limited eye movement with a median duration of symptoms of 2.1 months (IQR, 1–6.1 months). All patients had their diagnosis confirmed based on clinical manifestations and on the results of one of the following tests: a clinical response to a neostigmine test (18 tested patients) and a response to pyridostigmine (88 patients), positive repetitive facial nerve stimulation test result (20 of 32 tested patients), seropositive anti-AChR (6 of 8 tested patients), a positive ice pack test (85 of 93 tested patients), and a fatigue-induced ptosis test (107 of 109 tested patients). After diagnosis, 96 (83.5%) patients underwent chest imaging, and anterior mediastinal lesions were detected in 17 patients by performing contrast computed tomography, of whom 11 patients underwent thymectomy with pathological confirmation of thymus abnormalities, including thymoma ($n=6$), thymic hyperplasia ($n=4$), and malignant thymoma ($n=1$). During the follow-up visits, 6 patients with unremarkable chest imaging underwent thymectomy, and all of these pathologies involved thymic hyperplasia. Seropositive ANA was found in 9 of 48 (18.8%) patients, and 12 of 84 (14.3%) patients had abnormal thyroid function without thyroid-associated ophthalmopathy. Hyperthyroidism or rheumatoid arthritis, which are both autoimmune diseases, were identified in 8 and 1 patient, respectively.

Patients were initially treated based on clinical manifestations and were categorized according to treatment regimen prior to the onset of GMG, as shown in Table 1. The median time from onset to starting treatment was 2.1 (range, 1–6.1) months and there was no significant difference in the time to receiving treatment between the groups. Pyridostigmine was administered to all patients in the no-IMS group ($n=34$, 29.6%). Of 81 (70.4%) patients in the IMS group, 65 patients received various doses of corticosteroid (prednisolone, 5–70 mg per day), 4 patients received azathioprine alone (25–100 mg per day), and 12 patients received a combination of prednisolone and azathioprine. There were no significant differences in baseline characteristics or investigations between the treatment groups, except for ocular symptoms (Table 1). The incidence of both ptosis and diplopia was higher in the IMS treatment group, since the poor response to anticholinesterase was the basis for commencing immunosuppressants. After the diagnosis of GMG, 2 patients received intravenous immunoglobulin due to the rapid exacerbation of their symptoms. During the follow-up period, both patients with OMG and those with GMG who had been treated with IMS had various side-effects, such as the development of a cushingoid appearance ($n=18$), leukopenia or pancytopenia ($n=5$), opportunistic infection ($n=4$), gastrointestinal disturbance ($n=4$), ocular hypertension ($n=3$), cataract ($n=3$), rash ($n=2$), and uncontrolled blood sugar ($n=1$).

3.1. Risk of secondary generalized myasthenia gravis

Overall, 35 (30.4%) patients developed GMG during the follow-up. Figure 1-A summarizes the time-to-event data using the Kaplan–Meier method. The 2-year, 4-year, and 6-year cumulative probabilities of progressing to GMG were 23.7%, 32.6%, and 34.9%, respectively. The median time to GMG conversion was 2.9 (range, 1.4–5.5) years. At 2-year follow-up visit, 13 (11.3%) patients were lost to follow-up, leaving 67 patients in the OMG group, and only 28 patients underwent the 6-year follow-

up visit. In Figure 1B, the time-to-event was classified according to treatment regimen and showed significantly different GMG progression between the regimens ($P=.005$). The conversion rates at 2-year and 4-year follow-ups in patients with IMS were 16.9% and 25.3%, respectively, both of which were lower than those in patients without IMS (40.8% and 51.9%, respectively). The median time to developing GMG in the IMS treatment group (3.1 years) was longer than that in the non-IMS group (1.7 years). In Figure 1C and D, significantly different time-to-GMG progressions in relation to thymus status and RNS results were observed ($P < .001$).

Table 2 summarizes the results of the Cox proportional hazards regression analysis, which highlighted 3 statistically significant risk factors for developing GMG. Treatment with IMS significantly reduced the rate of GMG progression, with an adjusted hazard ratio (aHR) of 0.36 (95% confidence interval [CI] 0.15–0.84). Patients with thymic abnormalities had a higher conversion rate than those with normal thymus (aHR 4.28, 95% CI 1.91–9.61), and patients with a positive response to the repetitive nerve stimulation test were more likely to progress to GMG than those with negative results (aHR 3.84, 95% CI 0.83–17.75). Age group, signs and symptoms, ANA, and thyroid function test results were not significant predictors of GMG conversion.

4. Discussion

Our study reports the conversion rate and predictors for developing GMG in long-term follow-up patients with OMG in southern Thailand. In this study, patients treated with IMS had a longer GMG-free period than those not treated with IMS. This is an important finding in understanding the prognosis of OMG, which requires long-term follow-up to determine disease progression.

Regarding the demographic data, the mean age at OMG diagnosis in our study was 47.5 years old with a slightly higher prevalence of younger patients (≤ 50 years), which is similar to the age reported in a large retrospective study in Korea.^[13] A slight female predominance in our study has also been reported by other studies in Asia,^[13,19] in contrast to that of a population-based study with a higher male prevalence.^[24] The rate of secondary generalization at 2 years after onset in our study was 23.7%, which was similar to those of recent studies conducted in other Asian countries.^[13,18,19] However, our results were lower than those reported in certain Western countries, where conversion rates have been found to be in the range of 50%.^[14–17,20,21] We consider that the conversion rates varied among these studies because of the lack of a definitive diagnosis of myasthenia gravis, variations in demographic data, and the current widely used immunosuppressive therapy for preventing generalization. In terms of OMG diagnostic criteria, there is no single uniform test for disease confirmation. A positive serologic test was reported in 50% to 70% of patients with OMG^[25,26] and the RNS test results indicated a decremental response in only 19% to 33% of patients.^[27,28] We also included patients with a positive ice-pack test or a positive fatigue-induced ptosis test, and these tests have previously been reported to have a high sensitivity ($>80\%$).^[29–31] Therefore, using different diagnostic tests in several studies could have caused variations in the conversion rates. Currently, single-fiber electromyography (SFEMG) is the most sensitive test to diagnose OMG.^[27,28,32] This technique requires a special needle electrode, and our hospital lacks the

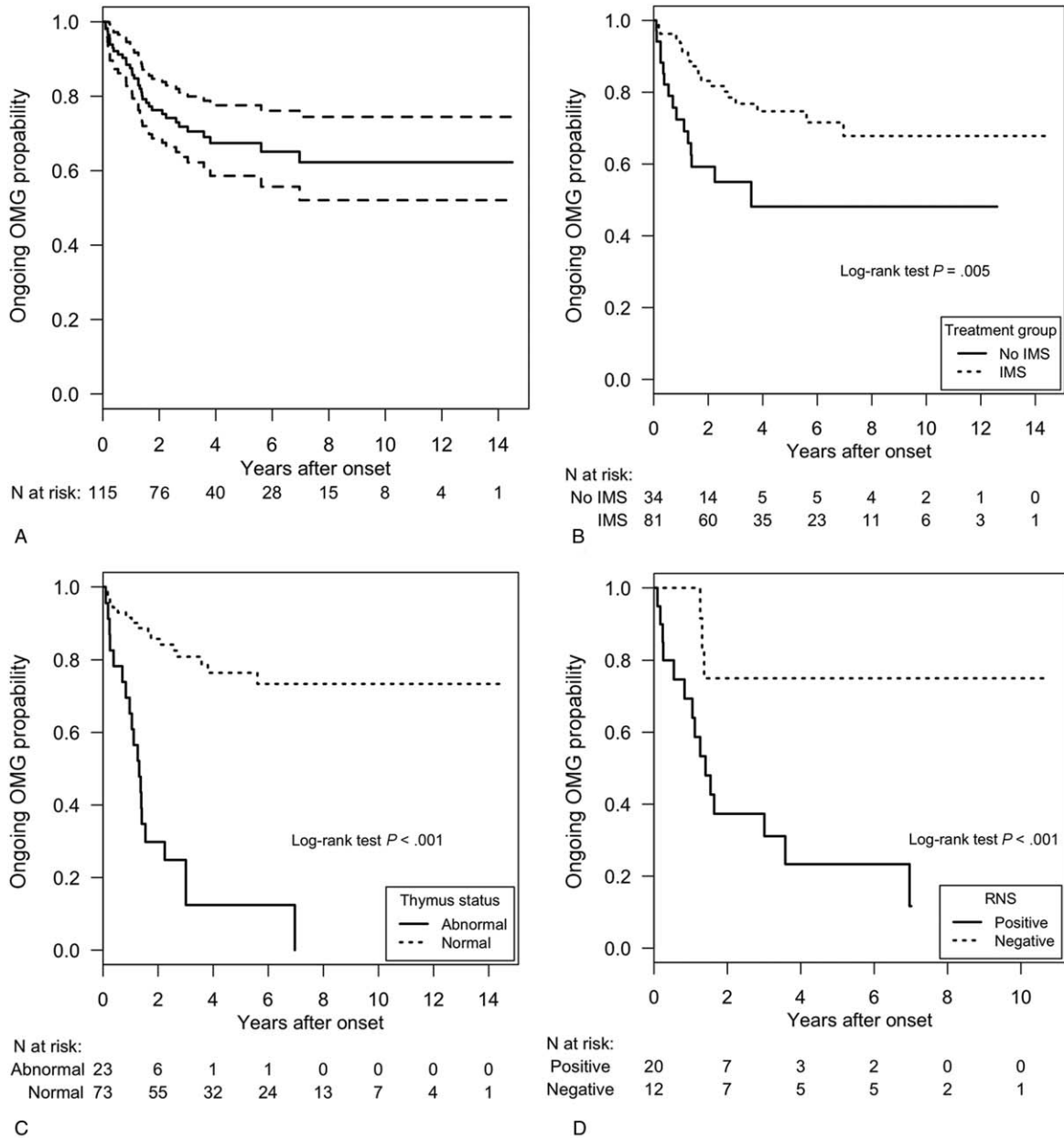


Figure 1. Kaplan–Meier curves (A) of the proportion of patients with ongoing ocular myasthenia gravis (OMG) in relation to years after onset; (B) between immunosuppressants (IMS) and no IMS; (C) of the thymus status; and (D) for repetitive nerve stimulation results (RNS).

Table 2
Multivariate Cox proportional hazards regression analysis of risk factors predicting GMG conversion.

Variable	Crude HR (95%CI)	Adjusted HR (95% CI)	P value (LR-test)
Age group: ≤ 50 vs > 50 years	2.75 (1.29,5.88)	2.07 (0.92,4.67)	.07
Ocular symptoms: ref. = ptosis			.41
Diplopia	3.65 (1.18,11.29)	0.42 (0.08,2.14)	
Both	1.54 (0.75,3.15)	1.19 (0.46,3.06)	
EOM: limited vs full	1.89 (0.97,3.68)	2.22 (0.93,5.3)	.07
Thymus: abnormal vs normal	7.68 (3.79,15.57)	4.28 (1.91,9.61)	< .001
RNS: positive vs negative	4.62 (1.33,16.01)	3.84 (0.83,17.75)	.04
ANA: positive vs negative	2.69 (1.1,6.6)	2.79 (0.82,9.45)	.28
TFT: abnormal vs normal	1.13 (0.39,3.25)	1.78 (0.48,6.57)	.62
Treatments: IMS vs no IMS	0.4 (0.2,0.78)	0.36 (0.15,0.84)	.02

ANA = antinuclear factor, CI = confidence interval, EOM = extraocular movement, HR = hazard ratio, IMS = immunosuppressants, RNS = repetitive nerve stimulation, TFT = thyroid function test.

single fiber recording capability. We recommend performing the SFEMG for the establishing OMG diagnosis in further studies. In addition, sex proportions and age may affect the rate of generalization. Our study had a predominance of female and younger patients (≤ 50 years), and several studies have reported that these patients have a high risk of progression to GMG.^[15,16,19] However, the prevalence of treatment with IMS in our study (70.4%) was higher than that in various recent studies (32.7%–63.2%).^[7,11,13,15,17–20,33] IMS treatment could have reduced the risk of developing generalization, based on the findings of previous studies.^[13,17]

The risk factors for developing GMG in our study were thymus abnormalities detected through chest imaging or pathology and positive repetitive facial nerve stimulation test results. Previous studies have reported thymoma, thymic hyperplasia, and seropositive AChR Ab to be strong predictors of generalization.^[10,13–19,21] In our study, the incidence of thymus abnormalities in OMG was found to be as low as 24%, which is similar to those of previous reports.^[13,18,19] Because of the low incidence of seropositive AChR Ab and the lack of testing capability in our hospital, we decided not to assess this potential risk factor, but we recommend including serology for predictor analysis in future research. We also found that a positive RNS result was associated with generalization, which was in accordance with previous reports.^[13,18,34] A possible explanation for this finding is that an abnormal RNS response at the limb muscles could help ophthalmologists diagnose subclinical types of GMG. In our study, we performed repetitive facial nerve stimulation testing at the nasalis or orbicularis oculi muscle, which would be positive for ocular myasthenia only and reduce bias in terms of limb muscle involvement.

A randomized controlled study evaluating the efficacy of corticosteroids found that patients treated with a placebo had a significantly higher incidence of treatment failure than those treated with prednisolone. However, the sample size was small, and the results of GMG conversion were inconclusive due to the short follow-up period (16 weeks).^[35] Moreover, previous retrospective studies have reported inconsistent findings concerning the benefit of receiving IMS for the prevention of GMG.^[13,17,18,20] Two studies found significantly lower rates of GMG in patients using a corticosteroid,^[13,17] whereas 2 other studies found no significant difference in conversion rates between treatment groups.^[18,20] Our study results indicated that treatment with IMS might reduce the rate of progression and delay the onset of GMG events. Based on previous reports, 80% to 90% of patients with OMG without immunosuppressive treatment developed secondary generalization within 2 years after onset without the likelihood of further progression.^[3,4,10] Our report found the median time of generalization in IMS treatment was 3.1 years compared with 1.7 years in the non-IMS group. We compared baseline characteristics and found no statistical differences between the treatment groups apart from ocular symptoms. We used multivariate analysis to adjust for the effects of other risk factors in developing GMG. Furthermore, we found mild side-effects associated with IMS treatment, such as cushingoid appearance, with patients rarely discontinuing medication. These findings provide evidence supporting the efficacy and safety of corticosteroids and azathioprine.

Our retrospective cohort study had some limitations, namely, missing data, potential selection bias from treatment preferences, lack of capability for performing the serologic test and SFEMG, and the small number of patients who had long-term monitoring.

Regardless of these limitations, our study findings indicated that treatment with IMS was clearly associated with reduced conversion to and delayed onset of GMG. Randomized controlled trials or prospective studies are needed to further support our findings.

In conclusion, our patients with OMG had a low risk of developing GMG 2 years after the onset of symptoms. Our study suggests that treatment with IMS can reduce the risk of the disease developing into a more severe GMG pattern and can also delay GMG onset. Long-term follow-up of >2 years is recommended in these patients to ensure that they remain in an OMG status. We found that thymus abnormalities and positive repetitive facial nerve stimulation test result were associated with higher odds of progression to GMG; thus, investigations for thymus abnormalities and tests for positive repetitive facial nerve stimulation test result should be performed routinely for patients with OMG.

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