

Clinical Features and Outcomes of Ocular Myasthenia Gravis in a Tertiary Philippine Hospital

Aubhugn T. Labiano, MD,¹ Franz Marie O. Cruz, MD^{1,2} and Bryan Vincent Q. Mesina, MD¹

¹Department of Ophthalmology and Visual Sciences, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines

²Peregrine Eye and Laser Institute, Makati, Philippines

ABSTRACT

Objectives. To describe the clinical profile and outcomes of a series of adult patients diagnosed with ocular myasthenia gravis and to evaluate the potential factors affecting the risk of generalization.

Methods. This retrospective cohort study involved a medical chart review of adult patients seen from 2012 to 2019 at the neuro-ophthalmology clinic of a tertiary Philippine hospital with a clinical diagnosis of ocular myasthenia gravis supported by serologic, electrophysiologic, or pharmacologic test results. Outcomes of interest were complete stable remission, pharmacologic remission, minimal manifestations, and generalization. Kaplan-Meier method and log-rank test were used to analyze the probability of generalization.

Results. The study sample consisted of 16 patients. The female to male ratio was 3:1. Mean age at symptom onset was 39 years. All patients received pharmacologic treatment, while two patients underwent thymectomy. No patient had remission as of last follow-up. Three patients had conversion of ocular myasthenia gravis to generalized myasthenia gravis. Mean time from symptom onset to generalization was 10.7 months. The generalization curves of patients who were symptomatic for less than two years and those who were symptomatic for at least two years prior to consult were significantly different ($p = 0.049$).

Conclusion. In this single-center study, there was female predominance among adult patients diagnosed with ocular myasthenia gravis. The incidence of generalization was 4 per 100 person-years while the 2-year probability of generalization was 30%. Further study is needed in order to determine the factors affecting the risk of generalization.

Keywords: *myasthenia gravis, pyridostigmine, Philippines*

INTRODUCTION

Myasthenia gravis (MG) is a rare autoimmune disorder of neuromuscular transmission resulting in weakness and fatigability of affected muscles.¹ Ocular myasthenia gravis (OMG) refers to the localized form of the disease involving one or a combination of muscles in the ocular region, which are the levator palpebrae superioris, extraocular muscles, and orbicularis oculi. OMG presents clinically as painless ptosis and/or any pattern of pupil-sparing ophthalmoplegia.² Weakness in eye closure may also be present.³ In contrast, generalized myasthenia gravis (GMG) is characterized by involvement of the bulbar, limb, or respiratory muscles.⁴ Previous studies reveal that the clinical pattern of MG varies geographically or by ethnicity. Among East Asians, the disorder tends to have earlier onset compared to Caucasians and is mainly the ocular type.⁵ In certain Asian populations,

Corresponding author: Franz Marie O. Cruz, MD
Department of Ophthalmology and Visual Sciences
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: focruz@up.edu.ph
ORCID: <https://orcid.org/0000-0002-2362-5658>

the conversion rate of OMG to GMG has been found to be lower than the rate among Caucasians.^{6,7} Genetic factors such as differences in the human leukocyte antigen system likely play a role in the observed variations in clinical manifestations.^{8,9}

Current knowledge about the general pattern of MG in the Philippines is limited. Published research is sparse, and country-specific population-based epidemiologic data on the disease do not exist. The purpose of this study was to describe the clinical profile and outcomes of a series of adult patients diagnosed with OMG in the neuro-ophthalmology clinic of a tertiary Philippine hospital. It also aimed to evaluate the potential association between clinico-demographic characteristics and the risk of conversion of OMG to GMG.

METHODS

This retrospective cohort study, which employed a review of medical records, was approved by the University of the Philippines Manila Research Ethics Board. The study was conducted in 2021. Medical charts of Filipino patients at least 18 years of age who were seen at the Neuro-ophthalmology Clinic of the University of the Philippines – Philippine General Hospital Department of Ophthalmology and Visual Sciences at some point from January 2012 to December 2019 and had a clinical diagnosis of ocular myasthenia gravis were reviewed. The diagnosis of OMG must have been affirmed by a neuro-ophthalmologist and supported by at least one of the following: (1) positive serologic test for MG-associated autoantibodies; (2) electrophysiologic test result/s consistent with MG; (3) positive edrophonium or neostigmine test; or (4) positive clinical response (i.e., improvement in ptosis or ophthalmoparesis) to pyridostigmine. Excluded from this study were patients who had signs and symptoms of GMG before, during, or within one month after initial consult, those who were symptomatic since birth, and those with missing records of their initial evaluation at the clinic.

Demographic and clinical data extracted from paper-based charts and electronic medical records included sex, age at symptom onset, ocular symptoms, symptom duration, previous consults, comorbidities, smoking history, neuro-ophthalmologic examination findings (i.e., presence of fatigability of sustained upgaze, Cogan lid twitch, enhancement of ptosis on elevation of the contralateral upper lid, and weakness of the orbicularis oculi), diagnostic tests ordered and their results, treatment instituted, and treatment outcomes.

Clinical outcomes as of the last clinic visit that were of interest and their definitions were the following:¹⁰

1. Complete stable remission: no symptoms or signs of MG for at least one year (except for isolated weakness of eyelid closure) and no treatment for MG during that time.
2. Pharmacologic remission: no symptoms or signs of MG for at least one year (except for isolated weakness of

eyelid closure) with pharmacologic treatment except for acetylcholinesterase inhibitors during that time.

3. Minimal manifestations: no symptoms of functional limitations but with some muscle weakness on examination (excluding isolated weakness of eyelid closure) while on treatment with acetylcholinesterase inhibitors, immunosuppressants or other symptomatic therapies.
4. Generalization: conversion of OMG to GMG.

Statistical Analyses

Descriptive statistics were computed for the various demographic and clinical characteristics. Subgroup univariate analyses, as appropriate, were performed using the Mann Whitney U test for continuous variables and the Fisher exact test for categorical variables. The generalization rate or conversion rate of OMG to GMG was computed among patients who had at least a 2-year interval between symptom onset and their last clinic visit. The cumulative probability of generalization was estimated using the Kaplan-Meier method. Log-rank test was utilized to analyze and identify the potential factors associated with generalization. The small study sample size precluded multivariate analyses of the predictors of generalization. Statistical analyses were performed using Stata/IC 13.1.¹¹ The level of significance was set at $\alpha = 0.05$.

RESULTS

The study sample consisted of 16 patients (Figure 1), 12 (75%) of which were female and 4 (25%) were male (Table 1). The overall female to male ratio was 3:1, and this female predominance persisted even when patients were divided in two groups based on age at onset of symptoms. Age at onset

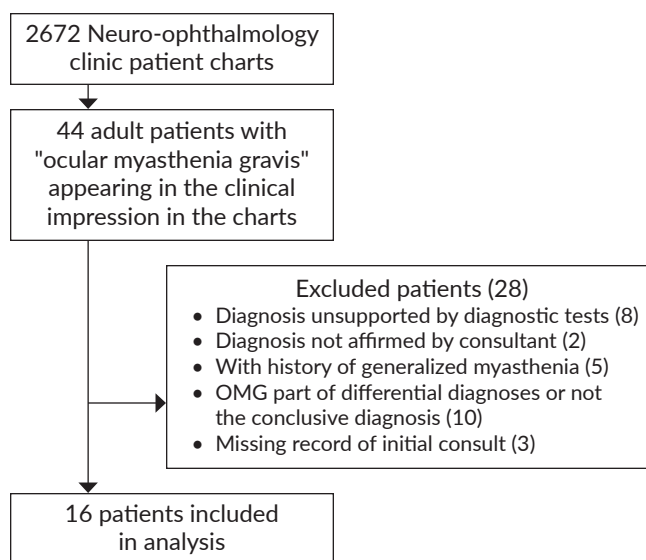


Figure 1. Patients included in and excluded from the study.

Table 1. Characteristics of Ocular Myasthenia Gravis Patients by Age at Symptom Onset

Variable	Total (n= 16)
Sex, n (%)	
Female	12 (75%)
Male	4 (25%)
Age at symptom onset (years)	
Mean $\pm$ SD	39 $\pm$ 11.15
Range	21 – 54
Interval between symptom onset and consult (years)	
Mean $\pm$ SD	3.5 $\pm$ 7
Range	0.625 – 25
Symptoms at disease onset, n (%)	
Diplopia only	0 (0%)
Ptosis only	5 (31%)
Diplopia and ptosis	11 (69%)
History of thyroid or autoimmune disease, n (%)	
Yes	4 (25%)
No	12 (75%)
Smoking history, n (%)	
Yes	4 (25%)
No	12 (75%)
Clinical exam findings, n (%)	
Isolated ptosis	7 (44%)
Isolated ophthalmoplegia	0 (0%)
Combined ptosis and ophthalmoplegia	9 (56%)
Signs of muscle fatigability or weakness, n (%)	
Cogan lid twitch, n=10	7 (70%)
Enhancement of ptosis, n=10	8 (80%)
Fatigability on prolonged upgaze, n=5	5 (100%)
Peek sign or orbicularis oculi weakness, n=4	1 (25%)
Electrophysiologic test	
Repetitive nerve stimulation, n=6	4 (67%)
Single-fiber electromyography, n=2	2 (100%)
Serologic test	
Acetylcholine receptor antibody, n=2	2 (100%)
Muscle-specific kinase antibody, n=1	0 (0%)
Pyridostigmine trial, n=14	14 (100%)
Abnormal chest imaging for thymoma	
Computed tomography scan, n=3	2 (67%)
Radiograph/X-ray, n=4	0 (0%)
Treatment regimen, n (%)	
Pharmacologic	16 (100%)
Pyridostigmine only	7 (44%)
Pyridostigmine + prednisone	5 (31%)
Pyridostigmine + azathioprine	1 (6%)
Pyridostigmine + prednisone + azathioprine	3 (19%)
Thymectomy	2 (13%)
Length of follow-up, months	
Mean $\pm$ SD	19.5 $\pm$ 29.68
Range	0.5 – 113
Clinical outcome as of last follow-up, n (%)	(n=10)
Complete stable remission	0 (0%)
Pharmacologic remission	0 (0%)
Minimal manifestation status	7 (70%)
Generalization	3 (30%)

SD – standard deviation

of symptoms was 39 years on average and ranged from 21 to 54 years. Thirteen (81%) of patients first developed symptoms before 50 years of age. The mean interval between onset of symptoms and first consult at the neuro-ophthalmologic clinic was 3.5 years. Eleven patients (69%) were seen at the clinic within one year from the onset of symptoms, while five patients (31%) had been experiencing symptoms for at least two years prior to neuro-ophthalmology consult.

All 16 patients had a history of ptosis or drooping of the upper eyelid. The ptosis was isolated in five patients (31%), while 11 (69%) had both ptosis and diplopia. No patient presented with diplopia only. Twelve patients (75%) had consulted with other medical professionals before they were seen at the clinic. Eight patients (50%) were also being managed by the Division of Adult Neurology in our institution. Four patients (25%) had a history of thyroid or autoimmune disease. These disorders were nontoxic goiter, Guillain-Barre syndrome, IgA nephropathy, and vitiligo. Four patients (25%) were current or former smokers.

During the initial clinic visit, 3 patients (19%) had unilateral ptosis while 13 (81%) had bilateral ptosis. Nine patients (56%) had bilateral eye movement limitation. Both ptosis and eye movement limitation were noted in 9 patients (56%). Evaluation of patients with suspected OMG entailed looking for signs of muscle fatigability or weakness. Cogan lid twitch was checked for in 10 patients and was observed in seven (70%). Evaluation for enhancement of ptosis as the contralateral lid was elevated was done in 10 patients, and eight (80%) had a positive finding. Only five of the 16 patients were assessed for fatigability of the levator on prolonged upgaze. Fatigability or an increase in the severity of ptosis was seen in all five patients (100%). Testing for orbicularis oculi muscle strength or checking for the peek sign was only done in four patients (25%). Only one was noted to have orbicularis oculi weakness.

Results of the different diagnostic tests done to support the diagnosis of OMG are also shown in Table 1. The ice test was done in 10 (63%) of the 16 patients, and seven had a positive ice test, indicating a test sensitivity 70%. The three patients with negative ice test results all had severe ptosis. The rest test and sleep test were not commonly performed. An electrophysiologic test was requested for 12 patients (75%) but was done in only 6 (50%) of them. Results from four (67%) of the six patients who underwent repetitive nerve stimulation (RNS) were suggestive of a neuromuscular disorder such as MG. Single-fiber electromyography (SF-EMG) was abnormal in all two patients who were able to have the test done. Serologic testing for autoantibodies implicated in MG was requested for five patients but was done in only three patients. Two patients tested positive for acetylcholine receptor antibodies (AChR Ab), while one patient tested negative for muscle-specific kinase antibodies (MuSK Ab). No patient underwent an edrophonium or a neostigmine test due to unavailability of the tests. As an alternative, a short-term trial with pyridostigmine was performed. Fourteen patients were

noted to have a positive response to pyridostigmine. Table 2 shows the diagnostic test inclusion criteria met by the patients in this study. Nine patients (56%) were included in the study because of only a positive response to a trial of pyridostigmine.

Imaging studies of the chest or anterior mediastinum to look for thymoma were ordered for 13 patients but only seven were able to have either a chest computed tomography (CT) scan or a radiograph (X-ray) done. Two of the three chest CT scans done showed an anterior mediastinal mass, possibly thymolipoma, while one scan only revealed mediastinal lymph nodes. None of the chest X-rays showed an anterior mediastinal mass.

All 16 patients were given pharmacologic treatment. Seven patients (44%) received pyridostigmine only, five (31%) received pyridostigmine and prednisone, one (6%) was on pyridostigmine and azathioprine, while three (31%) were on pyridostigmine, prednisone, and azathioprine at some point during their treatment. An adverse effect was reported in one patient who developed diarrhea after being on pyridostigmine at a dose of five 60-mg tablets per day. The two patients who were found to have anterior mediastinal masses on chest CT scan underwent thymectomy. Histopathologic examination revealed thymic hyperplasia ($n=1$) and unremarkable thymus ($n=1$).

Patients followed up in our institution for an average of 19.5 months. Shortest length of follow-up was two weeks while the longest was 113 months. Six patients (38%) followed up for at least 24 months. Of the 10 patients who had at least a 2-year interval between symptom onset and last follow-up, three patients had conversion of OMG to GMG. The 2-year generalization rate or conversion rate is 30% (Figure 2). Time to generalization was within 24 months after onset of symptoms in all three patients. Mean time to generalization was 10.7 months, and the median was seven months after symptom onset.

The incidence rate of generalization was also computed in person-years. This study has a total of 74.96 person-years and the computed incidence rate of generalization is 4 per 100 person-years. Results of the log-rank tests comparing Kaplan-Meier generalization curves when the patients are subdivided based on different demographic and clinical characteristics are reported in Table 3. The generalization curve of those who were symptomatic for less than two years prior to consult was significantly different from that of those who had symptoms for two or more years prior to consult in our institution ($p = 0.049$). For the other demographic and clinical parameters, either no significant difference between the curves of the subgroups was found or a comparison of Kaplan-Meier curves could not be made.

DISCUSSION

Myasthenia gravis is a clinical diagnosis made on the basis of clinical history and physical examination findings and supported by non-pharmacologic clinical, pharmacologic,

Table 2. Diagnostic Test Inclusion Criteria Met by Study Patients

Test result indicative of myasthenia gravis	n = 16
<i>Pyridostigmine trial only</i>	9
<i>Repetitive nerve stimulation only</i>	1
<i>Single-fiber electromyography only</i>	1
<i>Repetitive nerve stimulation + pyridostigmine trial</i>	2
<i>Single-fiber electromyography + pyridostigmine trial</i>	1
<i>Acetylcholine receptor antibody + pyridostigmine trial</i>	1
<i>Acetylcholine receptor antibody + repetitive nerve stimulation</i>	1

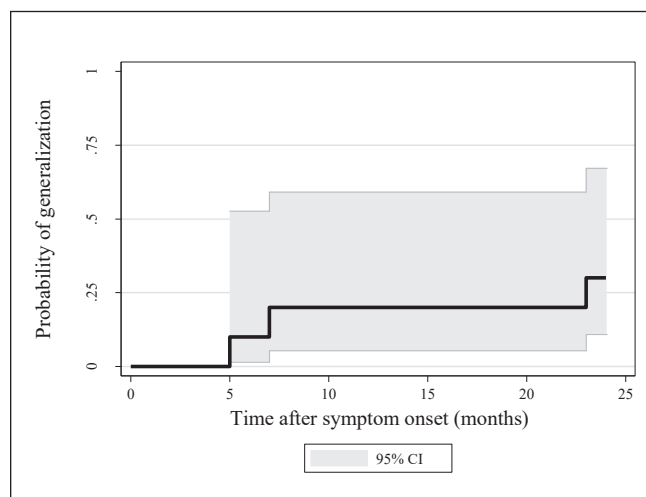


Figure 2. Kaplan-Meier curve depicting the cumulative probability of generalization of ocular myasthenia gravis over time.

electrophysiologic, serologic, and imaging tests. The estimated diagnostic accuracy of these tests, measured in terms of sensitivity and specificity, varies.² In MG, autoantibodies against acetylcholine receptors or other postsynaptic membrane constituents disrupt the normal structure and function of the neuromuscular junction.¹² Detection of serum acetylcholine receptor antibodies can be diagnostic of the disease, but there are rare situations of false-positive tests.¹³ In addition, only half of those with OMG test positive for these antibodies.¹⁴ At present, there is no widely accepted formal diagnostic criteria for MG as well as OMG.^{2,4} In this study, the diagnosis of ocular myasthenia gravis was made based on the presence of ocular signs and symptoms plus at least one positive diagnostic test. This may be a positive electrophysiologic test such as RNS or SF-EMG, a positive AchR Ab, or a positive response to an acetylcholinesterase inhibitor. Edrophonium and neostigmine tests are the conventional methods for the pharmacologic diagnosis of ocular myasthenia gravis. Administration of either drug in patients with myasthenia gravis results to transient improvement in the ptosis and/or diplopia with onset of

Table 3. Log-rank Test Results of Potential Factors Associated with Generalization

Variable	Number of patients with generalization/ total	p-value
Sex		0.4959
Female	2/8	
Male	1/2	
Symptom onset (years)		-
Early (≤ 50)	3/10	
Late (> 50)	-	
Interval between symptom onset and consult (years)		0.0494*
Interval < 2	3/5	
Interval ≥ 2	0/5	
Ptosis at presentation		0.3514
Bilateral	3/8	
Unilateral	0/2	
Extraocular movement limitation at presentation		0.3775
Absent	2/5	
Present	1/5	
History of thyroid or autoimmune disease		0.1173
Yes	0/4	
No	3/6	
Smoking history		0.2168
Yes	0/3	
No	3/7	
Thymus abnormality on chest imaging		0.3431
Yes	0/2	
No	2/5	
Repetitive nerve stimulation		0.4142
Normal	0/2	
Abnormal	1/3	
Acetylcholine receptor antibody		-
Positive	1/2	
Negative	-	
Prior prednisone treatment		0.2168
Yes	0/3	
No	3/7	

* $p < 0.05$

action within minutes which make them desirable office-based confirmatory tests. However, due to unavailability of the tests in the hospital, several patients received a 1- to 2-week trial of pyridostigmine, an oral form of acetylcholinesterase inhibitor that is also the first line treatment of myasthenia gravis. In this study, a positive response was considered diagnostic of ocular myasthenia gravis. All patients in this study had ptosis which made them good candidates for pyridostigmine trial as ptosis in myasthenia gravis is very responsive to the drug.¹⁵ Indeed, majority of patients in this study were included because they showed a positive response to pyridostigmine. A positive pyridostigmine test as a supporting evidence of ocular myasthenia gravis has also been used in a few published studies.^{6,16} In addition, Kim and Oh showed that in patients with clinical signs of ocular

myasthenia gravis, an unequivocal response to pyridostigmine is a useful and valid diagnostic test especially when antibody serology status is negative or unknown.¹⁷ However, a standard protocol on how to do a pyridostigmine trial does not exist in our institution, and study patients were prescribed varying doses of pyridostigmine. There are no published estimates on the sensitivity and specificity of the pyridostigmine test, but these are probably similar to the tests involving short-acting acetylcholinesterase inhibitors. The edrophonium test, for instance, has a reported sensitivity of 88–97% and specificity of 50–83% in diagnosing OMG while the reported sensitivity of neostigmine is 85%.^{14,16} A false positive result may be seen in cases of Lambert-Eaton myasthenic syndrome, botulism, snake envenomation, motor neuron disease, demyelinating disease, and intracranial mass,¹⁸ but none of these conditions were considered as possible diagnoses in the study patients on the basis of their clinical history and neuro-ophthalmologic examination findings.

Compared to other studies, this study's criteria for OMG were in the middle in terms of stringency. Some studies had more restrictive inclusion criteria such as requiring the performance of an electrophysiologic test in addition to a positive pharmacologic or serologic test, while other studies with less stringent criteria considered clinical signs such as fatigability on upgaze or clinical tests such as a positive ice test as supportive of the diagnosis of OMG.^{7,17,19–22} Requiring a positive diagnostic test in our screening criteria reduced our study sample size further (Figure 1), but this assured a more homogenous group. Patients diagnosed with ocular myasthenia gravis based on ocular symptoms alone but had negative diagnostic tests have a lower generalization rate compared to those who had at least one supporting evidence.²²

We compare our findings with those of OMG studies from Thailand, Singapore, and Korea, which had almost similar inclusion criteria to ours.^{7,17,23} Our cohort was predominantly female, similar to the cohort in Thailand. The patients in our study were younger when their symptoms started. The average or median age at symptom onset in these other Asian countries was above 40 years. Time from symptom onset to consult in our cohort was around 42.5 months, which was longer than the 8.4 months in Singapore. Majority of our patients had combined ptosis and diplopia on presentation, unlike in other countries where isolated ptosis or isolated diplopia was more common. None of our patients had isolated diplopia or extraocular movement limitation. We may be considering other etiologies and underdiagnosing OMG among patients with this clinical presentation.

Despite the small sample size, the 2-year conversion rate of OMG to GMG of 30% among our patients was within the reported generalization rates in literature.^{15,24,25} However, ours is higher compared to other Asian countries such as Singapore, Thailand, and South Korea with reported generalization rates of 8–23%.^{6,21,23,26} In light of the other studies that show ocular myasthenia gravis may convert to generalized disease at any time, we also computed for the

incidence rate of generalization in person-years.^{27,28} The incidence rate of generalization in this study was 4 per 100 person-years. This is lower than the cohort of Thai patients with AChR Ab-positive ocular myasthenia gravis at 14 out of 100 person-years.²⁹ Genetic factors and differences in the screening criteria and computation procedures may account for these disparities.^{6,21,23,26}

Univariate analysis revealed a higher probability of generalization among patients who were symptomatic for less than two years than among patients who were having symptoms for at least two years. This finding was consistent with previous research that showed that if MG remained purely ocular in two years then there was roughly a 90% chance that generalization would never occur.¹⁴ Factors associated with generalization identified in the Singapore study were anti-acetylcholine-receptor antibody positivity, abnormal repetitive nerve stimulation, and the presence of thymoma.⁷ Some retrospective studies suggest that steroids may prevent the conversion of OMG to GMG.^{20,24,30} We were unable to perform a rigorous multivariate analysis of the factors associated with conversion because of our small sample size and missing data. One of the two patients with positive acetylcholine receptor antibody test had conversion of OMG to GMG. The other patient did not develop GMG, but the thymectomy this patient underwent had likely modified the likelihood of generalization. Univariate analyses comparing Kaplan-Meier curves by repetitive nerve stimulation result, by the presence of a thymus abnormality on chest imaging, and by prior treatment with prednisone yielded *p*-values greater than 0.2.

This study had several limitations. Due to the retrospective chart review design, diagnostic evaluation, treatment, and record-keeping were not standardized. Inconsistencies in documentation may have resulted to the omission of important physical examination findings. Missing records and data were also a concern. As a result of the convenience sampling strategy employed, the study sample may not be representative of the population with ocular myasthenia gravis in the country. The limited sample size reduced the power of statistical tests. Potential sources of bias in the study include selection bias, which was minimized by applying strict diagnostic criteria that required at least one positive confirmatory test (electrophysiologic, serologic or pharmacologic) for ocular myasthenia gravis.

Despite these shortcomings, this paper is first to report the clinical profile and generalization rate of ocular myasthenia gravis among Filipino patients evaluated at a single referral hospital in the Philippines. This provides additional epidemiologic data in understanding the disease. Larger studies are needed to determine the factors that predict or modify the risk of generalization in this population.

CONCLUSION

This study described the clinical profile and outcomes of 16 patients with adult-onset ocular myasthenia gravis evaluated at the neuro-ophthalmology clinic of a tertiary Philippine hospital. There was female predominance among adult patients diagnosed with ocular myasthenia gravis. The incidence of generalization was 4 per 100 person-years. The 2-year probability of conversion of ocular myasthenia gravis to generalized myasthenia gravis was 30%. Further study is needed in order to determine the factors that predict or modify the risk of generalization.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

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