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Prognosis of Ocular Myasthenia Gravis

Retrospective Multicenter Analysis

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Purpose: To calculate the rate and timing of conversion from ocular myasthenia gravis to generalized myasthenia gravis.

Design: Retrospective multicenter analysis.

Subjects: Patients included in the study were diagnosed with ocular myasthenia gravis without the presence of generalized disease at onset.

Methods: We conducted a retrospective multicenter analysis. We reviewed charts of 158 patients who met diagnostic criteria for ocular myasthenia gravis. Patients were divided into 2 subgroups: an immunosuppressant treatment group and a nonimmunosuppressant treatment group. Timing of conversion to generalized disease and duration of follow-up also was evaluated. Additional data such as clinical symptoms at presentation, laboratory test results, and chest imaging results also were recorded.

Main Outcome Measures: Conversion rates to generalized myasthenia at 2 years, effect of immunosuppression on conversion, and timing of conversion.

Results: The 158-patient cohort included 76 patients who received immunosuppressant therapy; the remaining 82 patients did not. The overall conversion rate to generalized disease was 20.9%. At 2 years, generalized myasthenia developed in 8 of 76 patients in the treated group and in 15 of 82 patients in the nonimmunotherapy group (odds ratio, 0.52; 95% confidence interval, 0.20−1.32). Median time for conversion to generalized disease was 20 months in the nonimmunosuppressant group and 24 months in the immunosuppressant group. Conversion occurred after 2 years of symptom onset in 30% of patients.

Conclusions: Conversion rates from ocular to generalized myasthenia gravis may be lower than previously reported both in immunosuppressed and nonimmunosuppressed patients. A subset of patients may continue to convert to generalized disease beyond 2 years from onset of symptoms, and close monitoring should be continued. *Ophthalmology 2015;122:1517-1521 © 2015 by the American Academy of Ophthalmology.*

The pathophysiologic features of myasthenia gravis are related to autoimmunity directed against the acetylcholine receptor (AChR) of the neuromuscular junction, leading to reduced acetylcholine binding to its receptors and striated muscle weakness.[1] The initial presentation is limited to pure ocular symptoms (diplopia, ptosis, or both) in approximately 50% to 60% of cases.[2] Conversion rates from ocular myasthenia gravis (OMG) to generalized myasthenia gravis (GMG) traditionally are accepted to be in the range of 50% to 65%.[2−4] Prior reports indicate that more than 90% of OMG patients converting to GMG do so within 2 years.[2,3,5] More recently, Sommer et al[6] and Kupersmith et al[5] showed conversion rates of 31% and 36%, respectively, with rates as low as a 7%[5] in the subgroup of patients receiving immunosuppressive therapy followed up for a mean of 8.3 and 3.6 years. In addition, age, AChR antibody titers, and thymoma have been postulated to affect conversion rates.[2,5,6] We sought to calculate the rate and timing of conversion and to report on factors influencing conversion for our patient cohort.

Methods

We conducted a retrospective chart review of patients with OMG who sought treatment at the neuro-ophthalmology clinics of 6 practicing physicians at Michigan State University or the University of Michigan between 1993 and 2012. Approval for the study was granted by each institution's institutional review board before accessing patient medical records and abstracting data to an anonymized OMG database. Inclusion criteria consisted of age 18 years or older, 2 years or more of follow-up after diagnosis, and fulfilling our definition of OMG: the presence of diplopia, ptosis, or both (according to the criteria of Osserman and Genkins[7]) and at least 1 of the following: (1) positive acetylcholine receptor antibody (AChR Ab) titer, (2) significant jitter in single-fiber electromyography (sfEMG), or (3) unequivocal clinical response to edrophonium chloride (Tensilon test) or pyridostigmine. Exclusion criteria included history of prior or active thyroid eye disease, prior strabismus surgery, or GMG occurrence either at the onset of symptoms or within the first month of OMG. Generalized myasthenia gravis was defined as the development of symptoms or clinical findings such as dysphagia, dysarthria, dyspnea, or weakness of the face (except for orbicularis oculi), jaw, neck, or extremities. After OMG diagnosis, patients received acetylcholinesterase inhibitor treatment

http://dx.doi.org/10.1016/j.ophtha.2015.03.010
ISSN 0161-6420/15

Table 1. Background Features of Patients with Ocular Myasthenia Gravis

	All Patients (n = 158)	Nonimmunosuppressant Group (n = 82)	Immunosuppressant Group (n = 76)	P Value
Gender, no. (%)				0.49
Male	106 (67.1)	53 (64.6)	53 (69.7)	
Female	52 (32.9)	29 (35.4)	23 (30.3)	
Median age (IQR), yrs	61.5 (21)	61.5 (22)	61.5 (21)	0.57
Symptoms, no. (%)				
Diplopia	143 (90.5)	70 (85.4)	73 (96.1)	0.02
Ptosis	104 (65.8)	54 (65.9)	50 (65.8)	0.99
Both	89 (56)	41 (50)	48 (63.2)	
AChR Ab positive titer results, no. (%)	113/157 (72)	56/82 (68.3)	57/75 (76)	0.283
sfEMG pathologic response, no. (%)	51/59 (86.4)	24/29 (82.8)	27/30 (90)	0.47
Positive clinical results, no. (%)				
Tensilon test	21/21 (100)	8/8 (100)	13/13 (100)	—
Pyridostigmine	15/15 (100)	9/9 (100)	6/6 (100)	—
Presence of thymoma, no. (%)	8 (5.1)	6 (7.3)	2 (2.6)	0.27
Median follow-up (IQR), mos	60.5 (82)	64.5 (85.5)	57.5 (57.7)	0.34

AChR Ab = acetylcholine receptor antibody; IQR = interquartile range; sfEMG = single-fiber electromyography.

(pyridostigmine), immunosuppressive treatment (corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, plasmapheresis, or intravenous immunoglobulin [IVIG]), or no treatment at the individualized discretion of the treating physician. The following variables at clinical presentation were evaluated: age recorded in years, gender, clinical symptoms (diplopia, ptosis, or both), AChR antibody titer status, sfEMG response, clinical response to Tensilon test and pyridostigmine, presence of thymus pathologic features, and type of therapy. We evaluated duration of follow-up in months, conversion status (development of GMG), time to GMG conversion (calculated from time of symptom onset), and treatment method (immunosuppressant versus non-immunosuppressant therapy). Results of chest imaging, computed tomography, or magnetic resonance imaging were recorded.

For the statistical analysis, we used the chi-square square test (or Fisher exact test) and Mann−Whitney *U* test when comparing baseline variables between immunosuppressant and non-immunosuppressant treatment groups. The odds ratio (OR) of GMG developing at 2 years of follow-up was calculated for the different variables and was expressed with 95% confidence intervals (CIs). Univariate and multivariate logistic regression was performed to study the association between baseline variables and the development of conversion to GMG at 2 years. Kaplan-Meyer estimation was performed to evaluate the influence of treatment method, the presence of thymoma, and AChR antibody titer status on the time to conversion to GMG during the follow-up period. Univariate and multivariate proportional hazards regression analyses were used to determine the associations between baseline variables and the risk of conversion during the follow-up period. A *P* value less than 0.05 was considered significant. All data analyses were performed using SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY).

Results

One hundred fifty-eight patients with ocular myasthenia gravis fulfilling our inclusion or exclusion criteria were identified from our retrospective chart review. Of the 158 included, 106 (67.1%) were men and 52 (32.9%) were women, with a median age at onset of symptoms of 61.5 years (interquartile range, 21 years; range, 18−85 years) and a median follow-up period of 60.5 months (interquartile range, 82 months; range, 24−300 months). Of the 158 patients, diplopia alone was present in 54 patients (34%), ptosis alone in 15 patients (10%), and both symptoms coexisting in 89 patients (56%). Of the 158-subject cohort, testing included AChR antibody titer alone (77 patients); AChR antibody titer and sfEMG (59 patients); AChR antibody titer and edrophonium (Tensilon; 17 patients); AChR antibody, sfEMG and Tensilon test (4 patients); and only 1 patient classified by clinical response to pyridostigmine (no AChR antibody titer, sfEMG, or Tensilon test). Diagnosis of OMG was based on symptoms in combination with: (1) positive acetylcholine receptor antibody titer results in 113 (72%) of 157 patients tested, (2) abnormal sfEMG results in 51 (86.4%) of 59 patients tested, (3) clinical response to Tensilon test in all 21 patients tested, and (4) clinical response to pyridostigmine in all 9 patients tested. Thymoma was diagnosed by chest imaging in 8 (5.1%) of 158 patients, and thymectomy was performed in all 8; thymic hyperplasia was noted in 1 patient (0.6%). Patients were grouped further by treatment category: immunosuppressant treatment (IT) group or no immunosuppressant treatment (NIT) group (Table 1). The IT group contained 76 (48.1%) patients: corticosteroids, n = 50; mycophenolate, n = 14; azathioprine, n = 1; methotrexate, n = 1; corticosteroids in combination with mycophenolate, n = 5; corticosteroids in combination with mycophenolate and IVIG, n = 2; corticosteroids in combination with IVIG and plasmapheresis, n = 1; corticosteroids in combination with methotrexate, n = 1; and azathioprine in combination with cyclosporine, n = 1. The NIT group consisted of 82 (51.9%) patients: pyridostigmine, n = 77; prismatic lens n = 1; and no treatment, n = 4. Among the participating physicians, pyridostigmine was the first therapeutic choice in all patients, whereas prednisone, other immunosuppressive agents, or both were considered if lack of efficacy or side effects occurred. The median time to starting immunosuppressive therapy was 6 months. Except for the incidence of diplopia, which was more frequent in the NIT group ($P = 0.02$, chi-square test), there was no statistical difference in baseline characteristics between the 2 subgroups, including gender, age at the onset of symptoms, ptosis incidence, AChR abnormal titer results, abnormal sfEMG results, presence of thymoma, and follow-up duration (Table 1).

Of the 158 patients with OMG, 33 (20.9%) converted to GMG. Among these, 4 (12.1%) patients did so within the first 6 months, another 6 (18.1%; cumulative, 30.2%) within 1 year, 13 (39.3%;

Table 2. Risk for Conversion to Generalized Myasthenia Gravis by 2 Years

Risk Factor	Conversion to Generalized Myasthenia Gravis by 2 Years, No. (%)	*P* Value	Odds Ratio (95% Confidence Interval)
Gender		0.83	
Male	15/106 (14.2)		—
Female	44/52 (15.4)		1.10 (0.43–2.79)
Age (yrs)		0.22	
≤50	8/39 (20.5)		—
>50	15/119 (12.6)		0.55 (0.21–1.44)
AChR Ab titer results		0.08	
Negative	3/44 (6.8)		—
Positive	20/113 (17.7)		2.93 (0.82–10.44)
sfEMG response		0.29	
Normal	2/8 (25)		—
Abnormal	6/51 (11.8)		0.40 (0.06–2.45)
Thymoma		0.09	
Not present	20/150 (13.3)		—
Present	3/8 (37.5)		3.90 (0.86–17.59)
Treatment		0.16	
NIT	15/82 (18.3)		—
IT	8/76 (10.5)		0.52 (0.20–1.32)

AChR Ab = acetylcholine receptor antibody; IT = immunosuppressant therapy; NIT = no immunosuppressant therapy; sfEMG = single-fiber electromyography.

cumulative, 69.3%) during the second year, and the remaining 10 (30.3%) patients after 2 years. The median time to GMG conversion was 20 months (interquartile range, 36 months; range, 2–156 months). We did not observe a significant association between the risk for conversion to GMG and demographic or baseline factors, including gender, age younger than 50 years, and abnormal sfEMG results (Table 2). Patients with thymoma showed a trend for increased risk of conversion to GMG ($P = 0.09$, Fisher exact test; the OR for converting to GMG was 3.90 [95% CI, 0.86–17.59] compared with patients without thymoma). Patients with positive AChR antibody titer results showed a similar trend ($P = 0.08$, chi-square test; OR, 2.93; 95% CI, 0.82–10.44). Patients taking immunosuppressants evidenced the opposite trend ($P = 0.16$, chi-square test). In the first 2 years, although 15 (18.3%) of 82 patients in the NIT group converted to GMG, 8 (10.5%) of 76 patients in the IT group demonstrated GMG, corresponding to an OR of 0.52 (95% CI, 0.20–1.32).

Using a univariate logistic regression model to calculate the OR of GMG developing by 2 years according to gender, age, AChR antibody titer status, presence of thymoma, or use of immunosuppressants did not indicate significant effects. After controlling for the other factors in a multivariate model, no variable reached a significant association with the outcome (AChR antibody titer: OR, 3.34; 95% CI, 0.87–12.83; $P = 0.79$; presence of thymoma: OR, 2.59; 95% CI, 0.49–13.61; $P = 0.26$; use of nonimmunosuppressants: OR, 0.53; 95% CI, 0.20–1.38; $P = 0.19$).

The median time for conversion to GMG in the NIT group was 20 months (interquartile range [IQR], 17.2 months; range, 2–120 months), whereas in the IT group, it was 24 months (IR, 60 months; range, 3–156 months). In patients without thymoma, the median time for conversion to GMG was 18 months (IR, 39 months; range, 2–156 months), compared with 24 months in patients with thymoma (range, 20–24 months). In patients with negative AChR antibody titer results, the median time for

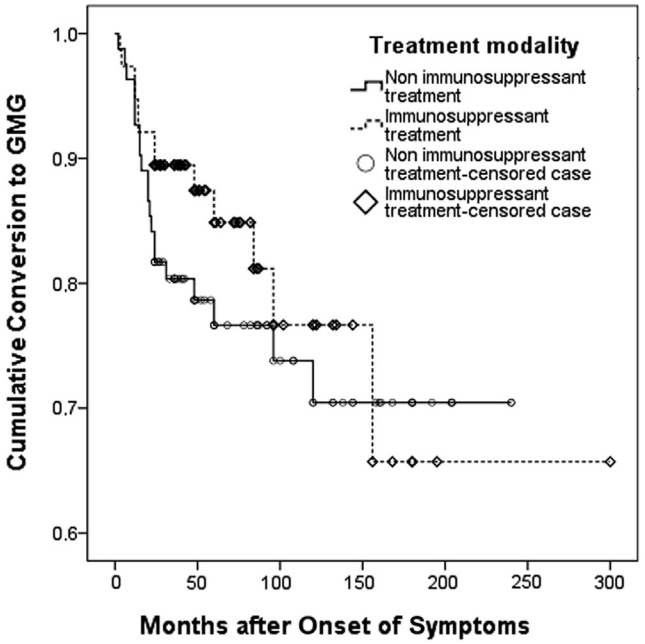

Figure 1. Kaplan-Meier curve of the cumulative conversion to generalized myasthenia gravis (GMG) after onset of symptoms in immunosuppressant-treated patients and nonimmunosuppressant-treated patients.

conversion to GMG was 34.5 months (IR, 92.2 months; range, 3–120 months), whereas in the positive AChR antibody titer results group, the median time for conversion to GMG was 20 months (IQR, 19 months; range, 2–156 months). The log-rank test did not reveal a significant difference in the rate of conversion to

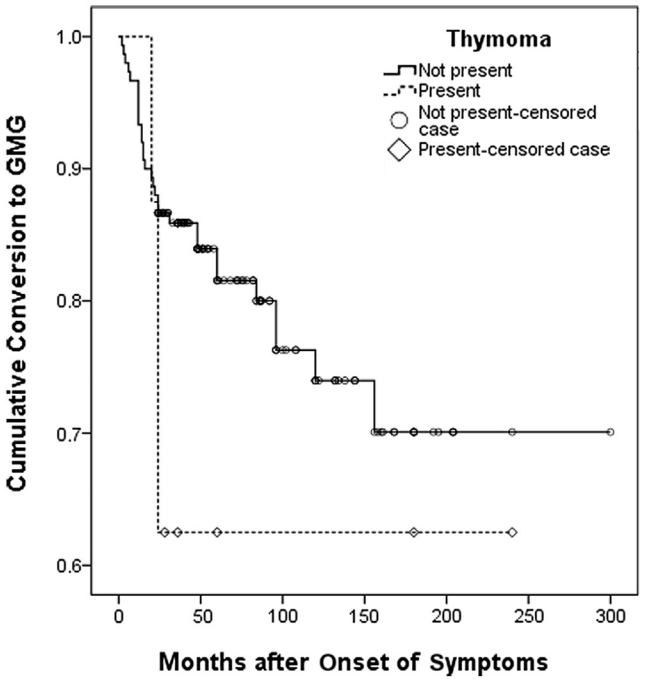

Figure 2. Kaplan-Meier curve of the cumulative conversion to generalized myasthenia gravis (GMG) after onset of symptoms in patients with and without thymoma.

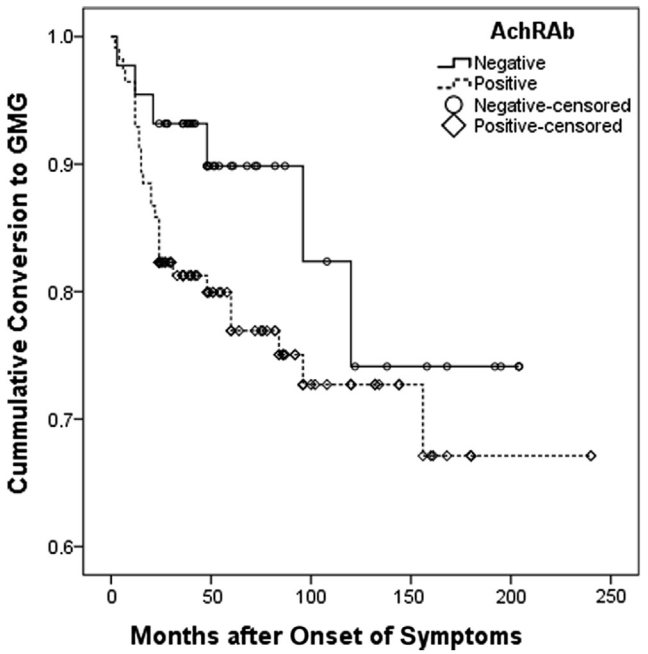

Figure 3. Kaplan-Meier curve of the cumulative conversion to generalized myasthenia gravis (GMG) after onset of symptoms in patients with negative and positive acetylcholine receptor antibody (AChR Ab) titer results.

GMG between the 2 treatment groups ($P = 0.37$), between patients with and without thymoma ($P = 0.28$), or between patients with positive versus negative AChR antibody titer results ($P = 0.17$; Figs 1, 2, and 3).

Univariate Cox proportional hazards regression analyses revealed that neither gender, actual age, presence of thymoma, AChR antibody titer status, or use of immunosuppressants significantly reduced the risk of conversion to GMG ($P = 0.61$, $P = 0.39$, $P = 0.29$, $P = 0.15$, and $P = 0.37$, respectively). Age, presence of thymoma, AChR antibody titer status, and use of immunosuppressants were not significant in the multivariate model, either.

Discussion

Our study, which included 158 patients with median follow-up of 60.5 months, represents a large, long-term, collaborative experience concerning conversion rates from OMG to GMG. Sommer et al[6] included 78 patients with mean disease duration of 8.3 years (99 months), Hong et al[8] presented 202 patients with a median follow-up period of 11.8 months, and Kupersmith et al[5] had 147 patients with mean follow-up of 3.6 years (43 months). With regard to demographics, our population had a male prevalence at 67%, with a median age at symptom onset of 61.5 years; comparatively, Sommer et al had a 51% male prevalence with a mean age at onset of 50.6 years, and Kupersmith et al had a 57% male prevalence with mean age at onset of 50 years. Eight patients (5.1%) in our OMG cohort harbored a thymoma, similar to previous reported incidence rates (0.7%[5] and 2.2%[9]). Regarding clinical features at presentation, 10% of our patients reported ptosis alone, 34% experienced only diplopia, and most, 56%, had both symptoms. AChR antibody titer was performed in most of our patient cohort (99%; n = 157), of which 72% had positive titer results. Previous studies have reported seropositive titers in OMG patients at a range of 35% to 100%.[5,6,8–10] Unlike the previous study by Kupersmith et al,[11] our IT and NIT subgroups had equal proportions of AChR antibody positivity, eliminating this variable when comparing conversion rates between the 2 groups.

Previous studies have shown overall conversion rates of OMG to GMG of 50% to 64%.[2,4,12,13] Our series of OMG patients showed a much lower overall conversion rate of 20.9%, consistent with more recent retrospective studies reporting overall conversion rates ranging from 23% to 31%,[6,8,14,15] and this low conversion rate was observed in subjects with or without immunosuppressant therapy. Prior studies have emphasized the possible effect of immunotherapy on conversion rates. Sommer et al[6] reported conversion of 12% in treated and 64% in untreated patients, and Kupersmith et al[5] reported a 7% conversion rate in the treated group versus 36% in patients not treated with prednisone. Monsul et al[16] reported conversion in 11% of the treated group and 34% of the untreated group at 2 years. Nonetheless, there are no randomized controlled studies to test this hypothesis, and in our series, the IT group had a 10.5% conversion rate (n = 76) compared with 18.3% conversions in the NIT group (n = 82; $P = 0.16$) within the first 2 years; the conversion rate in our NIT subgroup was notably lower than that reported previously in the literature.[2,4,12,13] Kaplan-Meier estimates comparing our IT and NIT groups showed no difference in cumulative conversion rates between the 2 groups in the first 18 months, or beyond 90 months from symptom onset.

No predictive factors for GMG conversion were found, including gender, age, or AChR-positive titer status, either in univariate and multivariate analysis. Interestingly, the presence of thymoma and AChR-positive titer showed a trend toward predicting conversion; however, this is small subgroup analysis. Previous retrospective studies have shown increased risk of conversion with AChR antibody positivity[5,8] and thymoma.[8] In our series, although the median age of our cohort was slightly older than that of the cohorts of Sommer et al and Kupersmith et al, age did not influence the outcome in the multivariate model. Previous reports have shown a trend toward frequent progression to the generalized form of myasthenia in older patients[17,18]; however, that did not occur in our series. Additionally, we point out that median age was balanced between our IT and NIT groups, eliminating age bias in the calculations of conversion rates.

Prior studies have noted that approximately 80% of patients converting to GMG will do so within the first year, and 90% within 3 years.[2,12,13] In contrast, our study showed 30% of patients converting within 1 year, 70% within 2 years, and 30% converted only after 2 years from symptom onset. Sommer et al[6] also noted 50% of their converting patients did so in the first 2 years, and 75% did so within 4 years.

As with any retrospective chart review, this study has its limitations in sample size, heterogeneity of treatment, and nonstandardized evaluation criteria; however, this multicenter experience involving several clinicians may better mirror disease characteristics and behavior in general. We

believe the clinical implications of these results are significant in several ways. First, the overall conversion rate from OMG to GMG is lower than previously reported, both in the immunosuppressed and nonimmunosuppressed cohorts. Second, caution should be taken in assuring patients that the risk of conversion after 2 years is minimal, and we believe that patients should continue to be monitored beyond the first 2 years. Additionally, trials evaluating immunosuppressant therapy for its effect on generalization need to take into account planned follow-up beyond 2 years; such studies also need to be powered for a lower generalization rate, factors that challenge large-scale feasibility especially given that many patients will receive immunosuppressant therapy for symptom control regardless of possible effects on generalization.

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Footnotes and Financial Disclosures

Originally received: November 26, 2014.
Final revision: February 27, 2015.
Accepted: March 10, 2015.
Available online: April 16, 2015. Manuscript no. 2014-1897.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

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Abbreviations and Acronyms:
AChR = acetylcholine receptor; **CI** = confidence interval; **GMG** = generalized myasthenia gravis; **IVIG** = intravenous immunoglobulin; **IQR** = interquartile range; **NIT** = no immunosuppressant treatment; **IT** = immunosuppressant treatment; **OMG** = ocular myasthenia gravis; **OR** = odds ratio; **sfEMG** = single-fiber electromyography.

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