Incidence, Epidemiology, and Transformation of Ocular Myasthenia Gravis: A Population-Based Study

TINA M. HENDRICKS, M. TARIQ BHATTI, DAVID O. HODGE, AND JOHN J. CHEN

• PURPOSE: To establish the incidence of ocular myasthenia gravis (OMG) as well as identify determinants of transformation to generalized myasthenia gravis (GMG) using a population-based record-linkage system.
• DESIGN: Population-based, retrospective cohort study.
• METHODS: All adults (≥18 years) diagnosed with myasthenia gravis (MG) from January 1, 1990, through December 31, 2017, were identified using the Rochester Epidemiology Project. Sixty-five patients with MG were identified. Data were collected regarding symptom onset, diagnostic testing results, and conversion from OMG to GMG.
• RESULTS: Median follow-up time was 91 months (range 17-333 months). The annual incidence of MG was 2.20/100 000 with a mean age at diagnosis of 59 years (SD =17) and 62% male sex. Thirty-three (51%) of the 65 patients presented with OMG, providing an annual incidence of 1.13/100 000. Eighteen (55%) of the 33 patients presenting with OMG converted to GMG at a median time of 13 months (range 2-180 months). Sixteen (67%) of 24 OMG patients who were seropositive for acetylcholine receptor antibody (AchR Ab) converted to GMG at 5 years compared to 11% (1/9) of those who were seronegative (hazard ratio [HR], 8.2, $P = .04$). Ten (77%) of 13 OMG patients with a positive single-fiber electromyography (sfEMG) at diagnosis converted to GMG at 5 years, compared with 18% (2/11) of patients who had a negative sfEMG (HR, 5.5, $P = .01$).
• CONCLUSIONS: In our population-based study, 51% (33/65) of patients with MG presented with isolated ocular involvement, with 55% (18/33) of these patients converting to GMG at some point in the course of their disease. Positive sfEMG and AchR Ab seropositivity at the time of diagnosis increased the risk of conversion to GMG. (Am J Ophthalmol 2019;205:99–105. © 2019 Elsevier Inc. All rights reserved.)

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From the Mayo Clinic Alix School of Medicine (T.M.H.), Department of Ophthalmology (M.T.B., J.J.C.), and Department of Neurology (M.T.B., J.J.C.), Mayo Clinic, Rochester, Minnesota; and Department of Health Sciences Research (D.O.H.), Mayo Clinic, Jacksonville, Florida, USA.

Inquiries to John J. Chen, Department of Ophthalmology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA; e-mail: chen.john@mayo.edu

MYASTHENIA GRAVIS (MG) IS AN UNCOMMON DISEASE in the adult population, with incidence reports ranging from 1.7-30 per million person-years.[1–3] In up to 85% of patients, the initial presenting symptom is related to the extraocular muscles, eyelids, or both, termed ocular MG (OMG).[4] The reported transformation rate of OMG to generalized MG (GMG) varies from 23.3% to 80%, depending on the setting in which the study has been performed.[4–7] All of these studies were done at academic centers and therefore may have suffered from a tertiary referral bias that influenced the true incidence and risk of disease progression. A population-based study focusing on the incidence of OMG has yet to be reported. The goal of this study was to establish this incidence, as well as identify risk factors for transformation to GMG, using the Rochester Epidemiology Project (REP).

METHODS

• PATIENT DATA: This retrospective cohort study was conducted using the REP database, a multicenter medical records linkage system designed to capture data from all patient-physician encounters in Olmsted County that allows population-based evaluation of diseases.[8] The medical records of all residents of Olmsted County, Minnesota, 18 years or older with newly diagnosed MG from January 1, 1990, to December 31, 2017, were identified using the REP by searching for MG, myasthenic syndrome, or OMG diagnoses. This study was approved by the Mayo Clinic and Olmsted County institutional review boards (IRB 17-010518 and 059-OMC-17, respectively). The medical records were individually reviewed to confirm the diagnosis of MG, determine residency of Olmsted County at time of diagnosis, and determine if patients presented initially with OMG or GMG. Patients who were referred to the institution but not residents of Olmsted County were excluded from consideration.

A diagnosis of OMG was defined by the presence of ptosis and/or diplopia with at least 1 of the following: (1) positive acetylcholine receptor antibody (AChR Ab) titer (AChR binding, blocking, or modulating), (2) significant jitter in single-fiber electromyography (sfEMG), or (3) unequivocal clinical response to edrophonium chloride (Tensilon test) or ice test. GMG was defined by any

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symptoms beyond the extraocular muscles or eyelid, including dysphagia, dysarthria, dyspnea, dysphonia, neck or extremity weakness with positive serologic or physiological testing. Results of diagnostic tests including Tensilon, sfEMG, AChR Ab titer, ice test, and Cogan eyelid twitch, as well as other factors such as the presence/absence of thymoma, thyroid status, thyroid eye disease, and treatments used were documented. During the time of this study, Tensilon was available and therefore neostigmine (Prostigmin) was not used as a diagnostic test. Enhancement of ptosis with manual elevation of the contralateral eyelid and orbicularis strength were not routinely documented and therefore were not included in the study. Conversion from OMG to GMG was documented, including date and time from initial diagnosis.

• **STATISTICAL ANALYSIS:** Descriptive statistics (eg, mean and percentages) were used to summarize the data. Categorical variables were compared between groups using the χ^2 test for independence. Baseline characteristics were compared between patients with OMG that remained isolated to the eyes and those that became generalized over time in order to investigate any factors associated with secondary generalization of OMG.

Age- and sex-specific incidence rates were calculated using the number of incident cases of OMG and all MG as the numerators and population estimates for Olmsted County residents age ≥50 years based on decennial census counts as the denominator; linear interpolation was used to estimate population size for intercensal years. Overall rates were age- and sex-adjusted to the 2010 US white population. Ninety-five percent confidence intervals (CIs) were computed for incidence rates assuming that the incident cases follow a Poisson distribution. Potential differences in the incidence between males and females were investigated with Poisson regression models. The conversation rate of the presenting ocular patients was estimated using the Kaplan-Meier method. Potential risk factors for conversion were evaluated using Cox proportional hazards models. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

THE MEDIAN FOLLOW-UP TIME WAS 91 MONTHS (RANGE 17-333 months). Sixty-five patients (40 male and 25 female) were diagnosed with MG, which provided an overall age- and sex-adjusted incidence of 2.20 per 100 000 per year (95% CI 1.66-2.75). The mean age of diagnosis was 59 years (standard deviation [SD]=17).

Overall, 51 (78%) of 65 patients had ocular symptoms at initial presentation and 60 (92%) of 65 had ocular symptoms at some point in their disease. Thirty-three (51%) of 65 patients presented with OMG according to our criteria.

TABLE 1. Demographic Information and Clinical Characteristics of Patients With Ocular and Generalized Myasthenia Gravis From 1990-2017 in Olmstead County, Minnesota

	Ocular	General	*P* Value
Total, n/N (%)	33/65 (51)	32/65 (49)	—
Age at diagnosis, mean (SD)	59 (16)	59 (19)	.92
Male	24 (73)	16 (50)	.06
Female	9 (27)	16 (50)	—
Race	(n = 33)	(n = 32)	—
White	29 (88)	25 (78)	.15
Asian	0 (0)	1 (3)	—
Black	2 (6)	0 (0)	—
Unknown	2 (6)	6	—
Eye findings on initial examination	(n = 33)	(n = 32)	<.001
Only diplopia	9 (27)	4 (13)	—
Only ptosis	7 (21)	3 (9)	—
Both	17 (52)	11 (34)	—
Neither	n/a	14 (44)	—
Eye findings ever in course	(n = 33)	(n = 32)	.03
Only diplopia	3 (9)	3 (9)	—
Only ptosis	4 (12)	8 (25)	—
Both	26 (79)	16 (50)	—
Neither	n/a	5 (16)	—
Seropositivity	(n = 33)	(n = 32)	—
Yes (AchR + striated)	27 (82)	28 (88)	.53
AchR only (AchR seropositive)	24 (73)	28 (88)	.14
Antibody type	(n = 27)	(n = 28)	—
AchR binding	23 (85)	27 (96)	.15
AchR modulating	18 (67)	24 (86)	.10
AchR blocking	1 (4)	8 (29)	.01
Striated muscle	18 (67)	15 (54)	.32
Evidence on single-fiber EMG	(n = 24)	(n = 23)	—
Positive	13 (54)	21 (91)	.004
Negative	11 (46)	2 (9)	—
Presence of thymoma	(n = 33)	(n = 32)	—
Yes	3 (9)	4 (13)	.66
No	30 (91)	28 (88)	
Thyroid status	(n = 33)	(n = 32)	—
Euthyroid	25 (76)	23 (72)	.26
Hypothyroid	6 (18)	9 (28)	—
Hyperthyroid	2 (6)	0 (0)	—
Hyperthyroid with thyroid eye disease	1 (3)	0 (0)	.32

Unless otherwise noted, values are n (%).
AchR = acetylcholine receptor; EMG = electromyography.

Age- and sex-adjusted incidence of OMG was 1.13 per 100 000 per year (95% CI 0.74-1.52). Among these 33 patients, the mean age at diagnosis was 58.8 years (SD=16), which was similar to those presenting with GMG (59.3 years, SD=18) (Table 1). In patients presenting with OMG, 24 (73%) of 33 were male, whereas an equal number of male and female patients presented with GMG (Table 1).

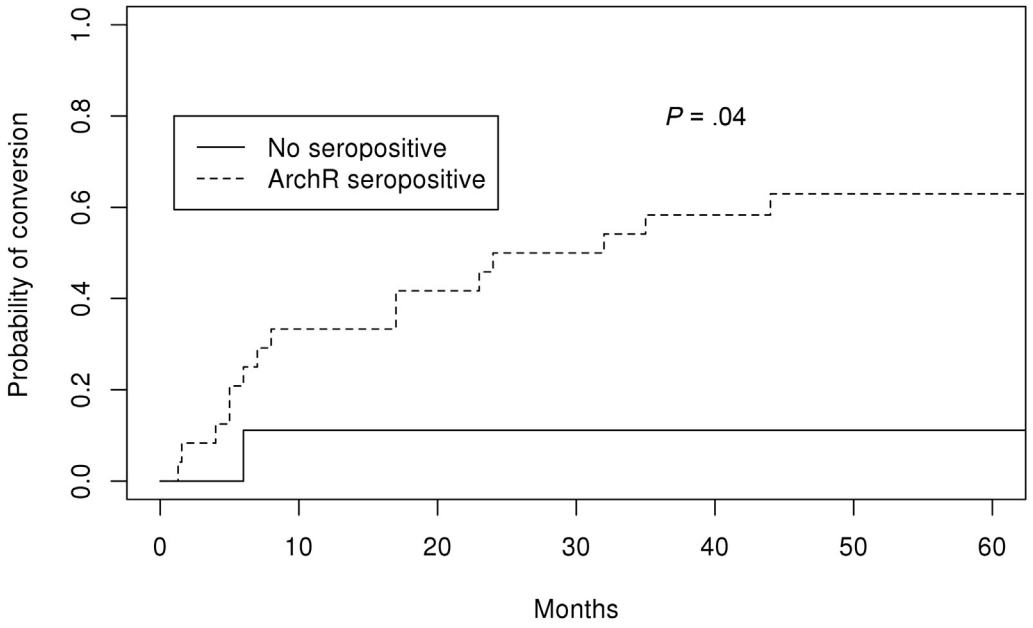

FIGURE 1. Kaplan-Meier curve depicting probability of conversion over time (months) from ocular to generalized myasthenia gravis in patients who were acetylcholine receptor antibody seropositive compared to those who were not.

Seventeen (52%) of 33 OMG patients presented with both ptosis and diplopia, whereas 16 (48%) of 33 had 1 symptom (27% diplopia and 21% ptosis). Among the 16 patients who presented with 1 symptom, 9 developed the second symptom at some point in their course and 7 (21%) of 33 remained isolated to their initial symptom (9% diplopia and 12% ptosis).

Overall, 35 (73%) of 48 MG patients had abnormal (increased mean consecutive difference, ie, jitter) sfEMG at presentation. Twenty-two (92%) of 24 patients presenting with GMG who were tested with sfEMG had an abnormal response compared with 13 (54%) of 24 patients presenting with OMG, $P = .003$.

Overall, 52 (80%) of 65 MG patients were AchR Ab seropositive (presence of AchR binding, blocking, or modulating Ab) at presentation. Twenty-eight of 32 (88%) of patients presenting with GMG were AchR Ab seropositive, compared with 24 of 33 (73%) OMG patients, $P = .14$ (Table 1).

Eighteen (54.5%) of 33 patients presenting with OMG converted to GMG at a median time of 13 months. Fifty percent (9/18) of those who generalized did so within 1 year, 72% (13/18) within 2 years, and 94% (17/18) within 5 years. AchR Ab seropositivity increased the risk of generalizing, with 67% (16/24) of seropositive patients converting to GMG at 5 years compared to 11% (1/9) of those who were seronegative(hazard ratio [HR] 8.2, 95% CI 1.1-61.6, $P = .04$) (Figure 1; Tables 2 and 3). SfEMG positivity was also associated with an increased risk of conversion, with 77% (10/13) of those with a positive sfEMG converting to GMG at 5 years compared with 18% (2/11) of patients who had a negative sfEMG (HR 5.5, 95% CI 1.5-20.7, $P = .01$) (Figure 2; Tables 2 and 3).

No other risk factor analyzed, including presence of thymoma (HR 2.48, 95% CI 0.7-8.71, $P = .16$), Tensilon test positivity (HR 3.29, 95% CI 0.41-26.42, $P = .26$), or immunosuppressive treatment significantly influenced conversion to GMG (HR 0.43, 95% CI 0.1-1.88, $P = .24$) (Tables 2 and 3). Of patients who were negative for both AchR seropositivity and sfEMG abnormality, none converted to GMG; however, there were only 4 patients in this category.

DISCUSSION

OUR STUDY, WHICH REPRESENTS THE FIRST POPULATION-based epidemiologic analysis of OMG, found an overall incidence of MG of 2.2 per 100 000 per year and an incidence of OMG of 1.13 per 100 000 per year. Previous MG epidemiologic studies have reported a large range of incidence from 0.17-7 per 100 000 per year.[1,9] Prior to this study, there had not been a population-based study focusing on OMG; however, population-based studies of MG have reported the percentage of populations presenting initially with solely ocular findings. In Cambridgeshire, England, of the 100 identified cases of MG, close to half (52%) of patients had ocular limited disease at presentation.[10] This percentage is similar to that in our cohort, in which 51% of MG patients presented with ocular MG.

TABLE 2. Demographic Information and Clinical Characteristics of Patients With Ocular Myasthenia Gravis Converting to Generalized Myasthenia Gravis From 1990-2017 in Olmstead County, Minnesota

	All	Remained Ocular	Become Generalized
Total, n/N (%)	33 (100)	15 (45)	18 (55)
Age at diagnosis, age (SD)	59 (16)	53 (14.2)	64 (16.8)
Male	24 (73)	10 (67)	14 (78)
Female	9 (27)	5 (33)	4 (22)
Eye findings on initial examination	(n = 33)	(n = 15)	(n = 18)
Only diplopia	9 (27)	3 (20)	6 (33)
Only ptosis	7 (21)	4 (27)	3 (17)
Both	17 (52)	8 (53)	9 (50)
Eye findings ever in course	(n = 33)	(n = 15)	(n = 18)
Only diplopia	3 (9)	1 (7)	2 (11)
Only ptosis	4 (12)	2 (13)	2 (11)
Both	26 (79)	12 (80)	14 (78)
Motility deficits	(n = 33)	(n = 15)	(n = 18)
Abduction	10 (30)	3 (20)	7 (39)
Adduction	9 (27)	3 (20)	6 (33)
Depression	8 (24)	4 (27)	4 (22)
Elevation	5 (15)	2 (13)	3 (17)
No motility deficit (full)	14 (42)	7 (47)	7 (39)
Alignment in primary gaze	(n = 33)	(n = 15)	(n = 18)
Hypertropia	23 (70)	9 (60)	14 (78)
Exotropia	8 (24)	3 (20)	5 (28)
Esotropia	7 (21)	2 (13)	5 (28)
Ortho	7 (21)	4 (27)	3 (17)
Seropositivity	(n = 33)	(n = 15)	(n = 18)
Yes (AchR + striated)	27 (82)	10 (67)	17 (94)
AchR only (AchR seropositive)	24 (73)	7 (47)	17 (94)
No (seronegative)	6 (18)	5 (33)	1 (6)
Antibody type	(n = 27)	(n = 15)	(n = 18)
AchR binding	23 (85)	7 (47)	16 (89)
AchR modulating	18 (67)	3 (20)	15 (83)
AchR blocking	1 (4)	0 (0)	1 (6)
Striated muscle	18 (67)	5 (33)	13 (72)
Evidence on single-fiber EMG	(n = 24)	(n = 11)	(n = 13)
Positive	13 (54)	3 (27)	10 (77)
Negative	11 (46)	8 (73)	3 (23)
Ice test	(n = 8)	(n = 4)	(n = 4)
Positive	7 (88)	3 (75)	4 (100)
Negative	1 (13)	1 (25)	0 (0)
Tensilon test	(n = 23)	(n = 12)	(n = 11)
Positive	19 (83)	9 (75)	10 (91)
Negative	4 (17)	3 (25)	1 (9)
Fatigability of ptosis	(n = 33)	(n = 15)	(n = 18)
Yes	29 (88)	12 (80)	17 (94)
No	4 (12)	3 (20)	1 (6)
Cogan eyelid twitch	(n = 5)	(n = 0)	(n = 5)
Positive	3 (60)	0 (0)	3 (60)
Negative	2 (40)	0 (0)	2 (40)
Presence of thymoma	(n = 33)	(n = 15)	(n = 18)
Yes	3 (9)	0 (0)	3 (17)
No	30 (91)	15 (100)	15 (83)
Thyroid status	(n = 33)	(n = 15)	(n = 18)
Euthyroid	25 (76)	11 (73)	14 (78)
Hypothyroid	6 (18)	2 (13)	4 (22)
Hyperthyroid	2 (6)	2 (13)	0 (0)
Hyperthyroid with thyroid eye disease	1 (3)	1 (7)	0 (0)

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TABLE 2. Demographic Information and Clinical Characteristics of Patients With Ocular Myasthenia Gravis Converting to Generalized Myasthenia Gravis From 1990-2017 in Olmstead County, Minnesota (*Continued*)

Unless otherwise noted, values are n (%).
AchR = acetylcholine receptor; EMG = electromyography.

With regard to demographics, our population had a male prevalence of 61.5% (40/65), which was driven by a higher male prevalence (73% [24/33]) among patients with OMG, whereas there was an equal number of male and female patients presenting with GMG. A slight male predominance in OMG has also been reported by others, but not all studies.[4,5,11–13] Age at diagnosis did not differ between OMG and GMG (both 59 years of age), which was similar to prior non–population-based studies.[12–14]

Overall, 78% (51/65) of MG patients in our population had ocular symptoms at initial presentation, with 92% (60/65) developing ocular manifestations at some point in their disease. Many others have reported similar findings, including Bever and associates[6] reporting ocular symptoms in 84% at onset and Grob and associates[4] reporting 85%.[11] In our cohort, 27% experienced only diplopia, 21% only ptosis, and 52% had both symptoms at initial presentation. Nagia and associates[12] reported similar findings, with 34% experiencing only diplopia, 10% only ptosis, and 56% both symptoms.

Fifty-five percent (18/33) of our cohort presenting with OMG converted to GMG. Prior studies have reported a wide range of conversion rates generally falling into a low and high range. Initial studies reported overall conversion rates of 50% to 64%.[4,6,11,15] More recent studies have described lower rates ranging from 21% to 31%, though many of these studies included a focus on the effect of immunosuppressive treatment.[5,12,14,16,17] One potential cause of a lower reported conversion rate in certain studies may be a shorter follow-up time. For example, Hong and associates reported a rate of 23.3% when following patients over a mean time of 11.8 months. At this same time point, the rate of conversion in our cohort was similar at 27% (9/33) (Figure 3), but increased to

TABLE 3. Risk Factors and Conversion Rate of Ocular to Generalized Myasthenia Gravis

Risk Factor	Hazard Ratio (95% Confidence Interval)	*P* Value
Immunosuppression	0.43 (0.10-1.88)	.26
AchR seropositivity	8.18 (1.09-61.61)	.04
AchR binding antibody	4.47 (1.03-19.50)	.05
AchR blocking antibody	2.67 (0.34-20.90)	.35
AchR modulating antibody	5.96 (1.72-20.74)	.005
Striational Ab seropositivity	2.83 (1.00-7.97)	.05
Presence of thymoma	2.48 (0.70-8.71)	.16
Pathologic thyroid status	0.85 (0.28-2.62)	.78
sfEMG pathologic response	5.57 (1.50-20.70)	.01
Positive clinical results		
Tensilon test	3.29 (0.41-26.42)	.26
Cogan eyelid twitch	1.80 (0.18-17.92)	.62

Ab = antibody; AchR = acetylcholine receptor; sfEMG = single-fiber electromyography.

52% (17/33) at 5 years. At final follow-up, a total of 23% (15/65) of our population remained OMG. This coincides with other population-based prevalence studies that report OMG accounting for upward of 20% of MG patients.[9,18–21]

Historically, it has been thought that nearly 80% of patients who generalize do so within the first year, and up to 90% within 3 years.[4,6,11] Among the 55% (18/33) OMG patients who generalized in our cohort, 50% (9/18) generalized within 1 year, 72% (13/18) within 2 years, and 94% (17/18) within 5 years, which is in line with recent studies suggesting that generalization can occur later in the course of the disease. Nagia and associates reported a median time of conversion of 20 months and found that 69.7% of the OMG patients who generalized did so within 2 years, but the remaining 30.3% converted after 2 years.[12] Sommer and associates and Antonini and associates found that 50% converted to GMG within 2 years and 60%-75% within 4 years.[14,22]

We found that an abnormal sfEMG and AchR Ab positivity at presentation increased the risk of transforming to GMG. Previous studies have also found an increased risk of conversion with AchR Ab positivity and a decreased risk of conversion with normal sfEMG testing.[5,13,23] Because sfEMG and AchR antibody represent tests with the highest sensitivity and specificity, respectively, for diagnosing OMG,[24] it is of interest that these tests also correlated with conversion to GMG. Our population showed no trend toward increased conversion with thymoma or thyroid derangements, despite these factors being shown to be significant or near significant by others.[5,12] Other investigators also have reported that immunosuppression may decrease conversion from OMG to GMG.[13,14,25] Although our study showed there was a trend toward decreased conversion with greater than 6 months of immunosuppression, the results were not significant possibly because of the small sample size.

There were several limitations to our study, including sample size, and a racially homogenous (white) cohort from a single geographic area. Owing to its retrospective nature, standardized evaluation and testing was not performed on every patient. For example, the presence or absence of a Cogan eyelid twitch was documented in a small percentage of patients, and therefore its sensitivity for OMG could not

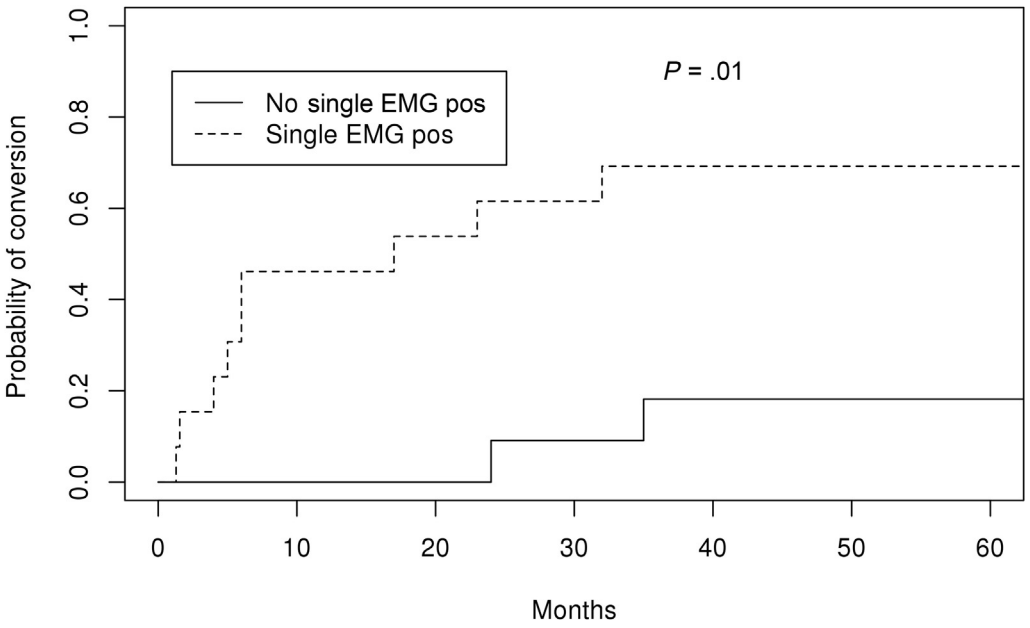

FIGURE 2. Kaplan-Meier curve depicting probability of conversion over time (months) from ocular to generalized myasthenia gravis in patients who had an abnormal single-fiber electromyography (EMG) test compared to those who were normal.

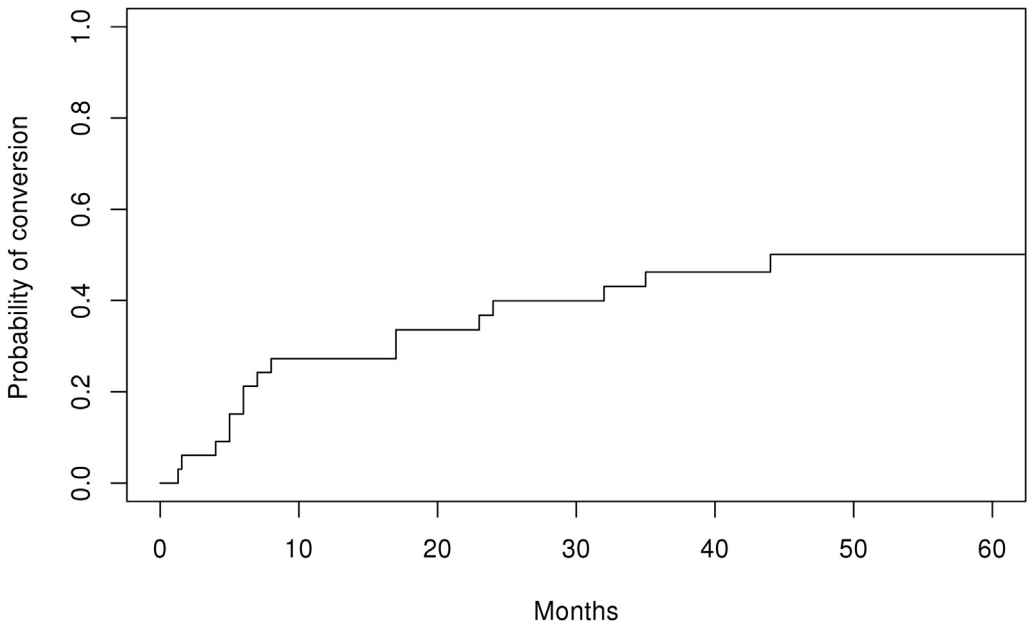

FIGURE 3. Kaplan-Meier curve depicting probability of conversion from ocular to generalized myasthenia gravis over time (months).

be evaluated. In addition, the small sample size could result in missing potential factors that could influence generalization, for example, immunosuppression.

In conclusion, this study represents the first population-based evaluation of OMG, which found an overall incidence of 1.13 cases per 100 000 per year. Fifty-one percent (33/65) of patients with MG presented with isolated ocular involvement, with 55% (18/33) of these patients converting to GMG. Twenty-eight percent (5/18) of patients transformed to GMG after 2 years into their disease course, challenging the traditional thinking that converting to GMG rarely occurs after 2 years. Abnormal sfEMG and AchR Ab seropositivity at the time of diagnosis increased the risk of conversion of OMG to GMG.

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The corresponding abstract will be presented at the 2019 North American Neuro-Ophthalmology Society meeting in Las Vegas, Nevada, USA.

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