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ORIGINAL ARTICLE

Late-onset generalized myasthenia gravis: clinical features, treatment, and outcome

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Abstract
Late-onset myasthenia gravis (LOMG) is a unique MG subgroup. More information is needed on its subgroups such as non-thymomatous generalized LOMG. We evaluated the effect of demographic, clinical, and serological factors as well as different immunosuppressive modalities on outcome in generalized non-thymomatous LOMG with onset ≥ 50 years. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification, MGFA postintervention score (MGFA PIS) and MG Composite scores were obtained to define the severity of disease and clinical outcome. In 95 patients with generalized non-thymomatous LOMG, 60 (63%) were men, 45 (47%) had mild disease, 80 (84%) were anti-AChR, and 56 (61%) were anti-titin positive. In those who received immunosuppressives and provided the clinical scores (84 patients), 50 (60%) had favorable outcome (MGFA PIS categories of complete stable remission, pharmacological remission and minimal manifestations) at the end of 3 years. Use of prednisone + azathioprine had significantly positive effect on outcome. The presence of anti-titin antibodies had no significant effect on severity and outcome. Five anti-MuSK-positive patients had favorable outcome. In conclusion, the presence of neither anti-titin nor anti-MuSK antibodies points to unfavorable outcome. Prednisone and azathioprine combination has beneficial effects in non-thymomatous generalized LOMG.

Keywords Myasthenia gravis · Late-onset · Elderly · Treatment

Introduction

Late-onset MG (LOMG) is different from early onset MG with respect to demographic–clinical characteristics [1–7] as well as serological properties [8] and HLA associations [9–12]. A lot of clinical information has been gathered on LOMG, particularly from studies with a large number of patients (Table 1) [1–7]. Although it is not easy to compare these studies because of the different cut-off ages chosen to distinguish LOMG from early onset MG (EOMG) and the variable inclusion of thymomatous MG, most of them reported a higher percentage each of men [1, 3, 4, 7], ocular MG [7], anti-acetylcholine receptor (-AChR) antibodies (ab) [3–5, 7], and anti-titin ab [5, 8, 13] in LOMG as compared to EOMG. However, very few of these studies gave satisfactory information on severity [1, 3, 4, 7] and treatment/prognosis [2–4] of LOMG. Furthermore, since ocular MG (consistently) and thymomatous MG (sometimes) have been included, it becomes impossible to find out in detail about the subgroups within LOMG which are quite different in these respects.

Our main aim was to evaluate the effect of demographic, clinical, and serological factors as well as different immunosuppressive modalities on outcome in a specific subgroup of patients among this cohort, namely those with generalized non-thymomatous LOMG followed for ≥ 3 years.

Materials and methods

All MG patients who applied for the first time to our Neuromuscular Outpatient Clinic between 2001 and 2010 (10 years) were considered for the study. Our MG database was used to identify the patients. These patients had fatigable muscle weakness and one or more of the following [14]:

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Table 1 Comparison of large late-onset MG (LOMG) cohorts (in studies consisting of ≥ 50 patients)

	Ref. [1]	Ref. [2]	Ref. [3]	Ref. [4][a]	Ref. [5]	Ref. [6]	Ref. [7]	Present study
Number of patients, *n*	55	113	172	183	88	83	114	179
Thymoma excluded/treated separately	No	No	No	No	Yes	Yes	No	Yes
Onset age	50	60	60	50	40	50	50	50
Females (%)	29	50	34	41	50	58	38	37
Anti-AChR positive (%)	82	ND	91	86	88	64	85	81
Anti-titin positive (%)	ND	ND	ND	ND	58	32	ND	61
Intubation (%)	36	ND	8.7	11	ND	4	8	6[b]
Outcome (remission + improved) (%)	87	87–93	81[c]	81	ND	ND	ND	87[b]

ND not done, *Ref* reference

[a]Patients in this cohort (collected before 1999) do not overlap with those in the 'present study' which included first-comers between 2001 and 2010

[b]In patients followed for ≥ 3 years

[c]The number given is for all immunosuppressed patients; it was 89% for those taking prednisone and azathioprine. The number was 77% for the whole group

(1) unequivocally positive response to anticholinesterases, (2) presence of serum anti-AChR or muscle-specific kinase (MuSK) ab, and (3) decrement of > 10% on repetitive nerve stimulation or abnormal jitter or blocking on single-fiber EMG.

The study group included patients with LOMG followed for ≥ 3 years (Fig. 1). In the present study, late-onset was defined as non-thymomatous MG with onset at ≥ 50 years of age [15, 16]. The term generalized LOMG is used for generalized non-thymomatous MG with anti-AChR, anti-MuSK ab, or without identified ab (seronegative MG). Ocular MG was excluded. Since generalization usually occurs within 3 years in MG with onset in ocular muscles [17], the choice of 3 years enabled us to exclude those patients who had purely ocular symptoms within this time period, deserving to be designated as ocular MG.

Ninety-five patients with generalized LOMG had been followed for ≥ 3 years. Attempt was made to reach all of the generalized LOMG patients by phone calls or by letters. Eighty patients responded and 65 of them came to the outpatient clinic for re-evaluation. Information from patient relatives contacted revealed that eleven patients had died: one because of MG and ten because of other reasons (Fig. 1).

Information on gender, onset age, onset symptom, serological characteristics, and disease severity was extracted from the medical records in all patients. Patients who agreed to come were examined in detail and missing data were completed. Maximum Myasthenia Gravis Foundation of America (MGFA) Clinical Classification and MGFA postintervention score (MGFA PIS) [18] were determined (mutual consent of two neurologists, SYC and FD), and MG Composite scores [19] (performed by SYC) were obtained. Thus, we were able to re-evaluate some patients at the end of 3 years and others at the end of follow-up if they had been followed for a longer period. Although the main objective of the study was to evaluate the factors affecting outcome at the end of 3 years, evaluating patients with longer follow-up gave us a chance to see how they progressed to the end of follow-up and to complete missing antibodies and missing data in the medical records.

All of the 95 patients were tested for anti-AChR ab and all anti-AChR negative patients for anti-MuSK ab by radioimmunoassay. Anti-titin ab were tested (by the ELISA method) in those followed for ≥ 3 years, to make certain that only generalized MG patients were included.

Association between immunosuppressive treatment and outcome was evaluated in 84 patients (Fig. 1). The effect of immunosuppressive modalities (prednisone [PRED] only, azathioprine [AZA] only, PRED + AZA) was evaluated at the end of 3 years of immunosuppressive treatment and at the end of follow-up. To be accepted as a user, the patients should have received PRED for at least 6 months and AZA for at least 12 months. MGFA PIS was used to define the outcome. MGFA PIS favorable outcome included categories of 'complete stable remission (CSR), pharmacological remission (PR), and minimal manifestations (MM)' for 1 year. Unfavorable outcome included categories of 'improved (I), unchanged (U), worse (W), exacerbation (E), and died of MG (D of MG)'. Patients with favorable outcome should not have received intravenous immunoglobulins (IVIg) or plasma exchange for the past 1 year.

MG composite score was obtained in those patients who we were able to reach and re-evaluate at our outpatient clinic. Score of ≤ 3 was accepted as mild and > 3 as moderate–severe disease.

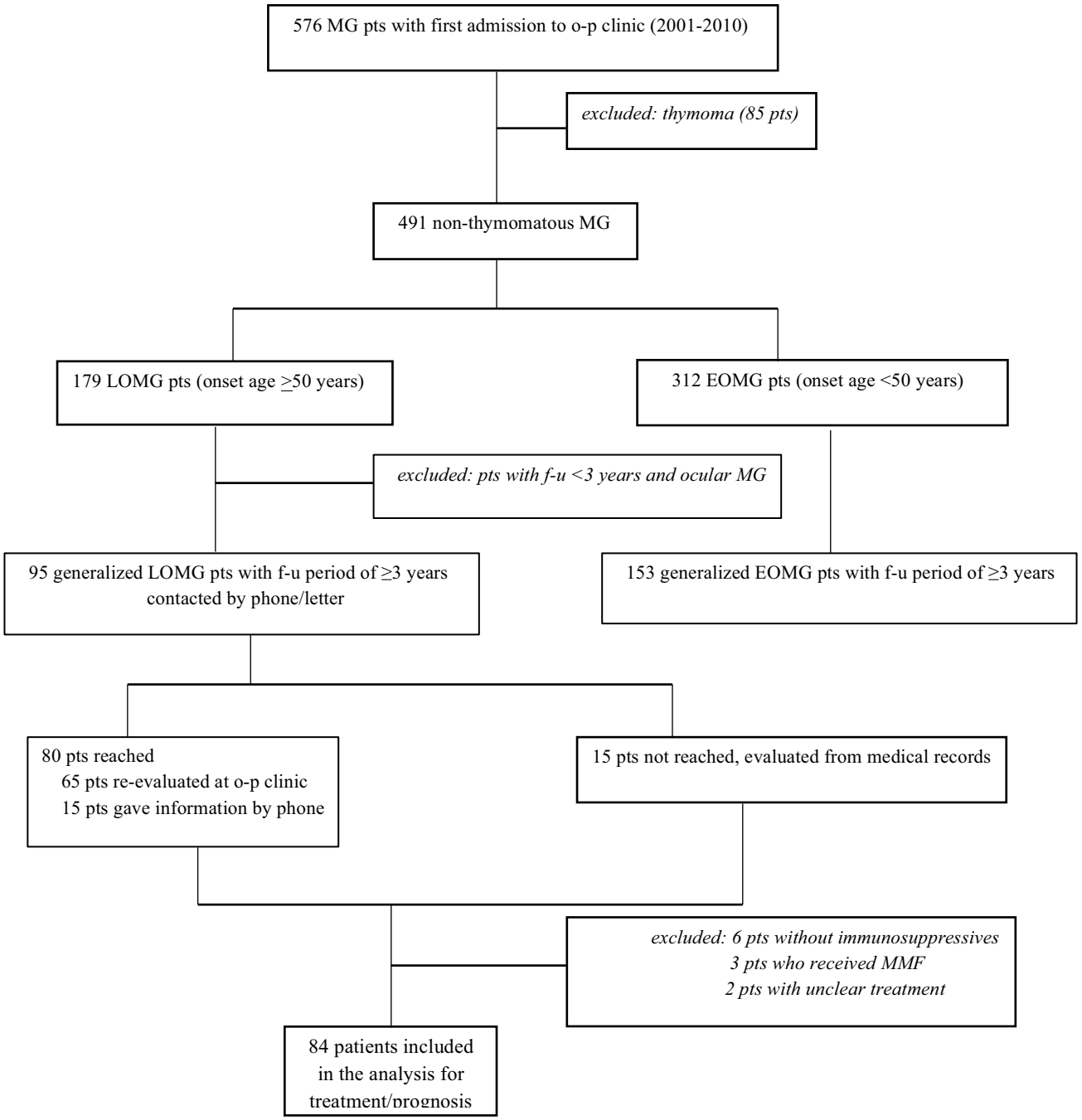

Fig. 1 Flowchart for the study including treatment/prognosis evaluation for late-onset MG (LOMG)

Statistical analysis

Distribution of data was determined by Shapiro–Wilk test. Continuous variables were expressed as mean (± standard deviation) or median (minimum–maximum), and categorical variables as frequency and percent. Continuous variables were compared with the Mann–Whitney *U* test and categorical variables with Pearson's Chi-square test or Fisher's exact Chi-square test. Patients who used immunosuppressive treatment (PRED and/or AZA), followed for ≥ 3 years, were included in the logistic regression analysis. Dependent variables were: (1) MGFA PIS at the end of 3 years of immunosuppressive treatment and (2) MGFA PIS at the last visit. Independent variables included gender,

disease onset age, serological status (anti-AChR, -MuSK ab, -titin), maximum disease severity (maximum MGFA Class), treatment modality (PRED only, AZA only, PRED + AZA), and presence of thymectomy. Kappa statistics was used to assess the correlation between MGFA PIS and MG Composite scores. Significance was set at $p < 0.05$ for all tests. Statistical analyses were performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of generalized LOMG

Sixty-three percent of the ninety-five generalized LOMG patients were men (female/male ratio: 0.6). The most frequent onset symptom was by far ocular (62%). Bulbar onset was the second most frequent symptom (23%). Extremity onset was infrequent (15%). Of the 59 patients with ocular onset, generalization occurred after 2 years in nine and after 3 years (5–7 years) in four patients. Information on the generalized LOMG patients (including that for the decades) is given in Table 2.

Close to one-half of the patients had mild disease (maximum MGFA Class 2) and a similar percentage had moderate–severe disease (maximum MGFA Class 3 in 35%, and MGFA Class 4 in 12%). In addition, 6% required mechanical ventilation (maximum MGFA Class 5).

The majority of the patients had anti-AChR ab which were very high in the 7 and 8 decades. There were only five anti-MuSK positive patients (three women and two men). Onset symptoms were bulbar (including one with head drop) in all of the anti-MuSK positive patients. Maximum MGFA Class was 2 in one, 3 in three, and 4 in one. MGFA PIS was favorable in all of them.

Anti-titin ab, performed in 92 patients, was positive in 61%. Their percentage was the highest in the 8 decades. All of the anti-titin ab positive patients were anti-AChR positive. When those with positive and negative anti-titin ab were compared, mild disease (maximum MGFA Class 2) was present in 51% of the positive group and 46% of the negative group ($p = 0.571$).

Thyroid disease was the most frequent autoimmune disorder, being present in fourteen patients (15%). Ten had Hashimoto thyroiditis, two had Basedow–Graves disease, and two had thyroid carcinoma. Other associated autoimmune disorders (one patient each) were pernicious anemia, polymyalgia rheumatica, psoriasis, and rheumatoid arthritis.

Table 2 Characteristics of late-onset MG (LOMG) in patients followed for ≥ 3 years (according to decades and in the whole cohort)

	6 decade	7 decade	8 decade	Total
Number of patients, *n* (%)	38 (40)	36 (38)	21 (22)	95
Gender, *n* (%)				
Female	14 (37)	12 (33)	9 (43)	35 (37)
Male	24 (63)	24 (67)	11 (57)	60 (63)
Onset symptom, *n* (%)				
Ocular	26 (68)	19 (53)	14 (67)	59 (62)
Bulbar	9 (24)	8 (22)	5 (24)	22 (23)
Extremity	3 (8)	9 (25)	2 (9)	14 (15)
Antibody, *n* (%)				
Anti-AChR positive	28 (74)	33 (92)	19 (90)	80 (84)
Anti-MuSK positive	3 (8)	1 (3)	1 (5)	5 (5)
Seronegative	7 (18)	2 (5)	1 (5)	10 (11)
Anti-titin antibody[a], *n* (%)				
Positive	20 (54)	21 (58)	15 (79)	56 (61)
Negative	17 (46)	15 (42)	4 (21)	36 (39)
Maximum MGFA, *n* (%)				
Class 2	18 (47)	18 (50)	9 (43)	45 (47)
Class 3, 4	18 (47)	16 (44)	10 (48)	44 (47)
Class 5 (intubation)	2 (6)	2 (6)	2 (9)	6 (6)

[a]Thirty-seven patients in 6 decade, 36 in 7 decade, and 19 in 8 decade tested for anti-titin antibodies

Evaluation of immunosuppressives in generalized LOMG patients

Six patients (1 woman and 5 men) had not received immunosuppressives (median follow-up 6 years; minimum 3 years; maximum 11 years). All of the six patients were anti-AChR ab positive. Anti-titin ab were positive in two of the patients. Three of the patients had mild disease (maximum MGFA Class 2). Two of the patients had undergone thymectomy. MGFA PIS was favorable in one and unfavorable in five of the patients.

Three patients had used mycophenolate mofetil in combination with PRED. Treatment was not clear in two other patients. Thus, immunosuppressives including PRED and AZA had been given to 84 patients (31 women and 53 men) who comprised the group in whom the effect of treatment modalities on outcome was evaluated (Fig. 1).

Evaluation at the end of 3 years of follow-up

The following immunosuppressives had been given to 84 patients: PRED only to 22 patients, AZA only to 12 patients, PRED+AZA to 50 patients. Maximum PRED dose was 30–60 mg/day, and maximum AZA dose was 100–200 mg/day. Nine patients had been thymectomized. MGFA PIS was favorable (CSR, PR, MM) in 59.5%. Mean maintenance PRED dose was 6.01±4.89 mg/day in those with favorable outcome and 11.19 ± 10.55 mg/day in those with

unfavorable outcome. Twenty-five patients (30%) were in the MGFA PIS category 'Improved' (I).

On univariate analysis, only the use of PRED+AZA as compared to the use of each agent alone was found to be significant ($p = 0.032$). The prognostic factors evaluated at the end of 3 years are given in Table 3. On logistic regression analysis, the use of PRED + AZA ($p = 0.009$) had significantly positive effect on outcome.

Twenty-five patients had been given a low maximum dose of PRED (≤ 30 mg). Twenty-one had maximum MGFA Class 2. Fourteen patients had received additional AZA. Nineteen of these patients (76%) had a favorable outcome. Mean maintenance dose of these patients was 6.7±5.94 mg/day.

Evaluation at the last visit

Median follow-up period until the last visit was 6 years (3–12 years). At the last visit, the following immunosuppressives had been given to 84 patients: PRED only to 16 patients, AZA only to 12 patients, and PRED + AZA to 56 patients. Maximum PRED dose was 30–60 mg/day; maximum AZA dose was 100–200 mg/day. Twelve patients had been thymectomized. MGFA PIS was favorable (CSR, PR, MM) in 63%. Mean maintenance PRED dose was 4.89 ± 5.08 mg/day in those with favorable outcome and 9.71 ± 10.32 mg/day in those with unfavorable outcome. Twenty patients (24%) were in the MGFA PIS category 'Improved' (I).

There was no significant factor effective on the final outcome, either by univariate analysis or by logistic regression analysis. The prognostic factors evaluated at the final outcome are given in Table 4.

Of the 24 patients with low maximum dose of PRED (≤ 30 mg), 19 had maximum MGFA Class 2. Twelve patients had received additional AZA. Fifteen of these patients (63%) had a favorable outcome. Mean maintenance dose of these patients was 4.37 ± 3.77 mg/day.

Table 3 Prognostic factors affecting outcome in late-onset (LOMG) at the end of 3 years of immunosuppressive treatment

	Favorable prognosis	Unfavorable prognosis	Significance* (*p*)
Number of patients, *n* (%)	50 (59.5)	34 (40.5)	
Gender, *n* (%)			0.629
Female	20 (40)	11 (32)	
Male	30 (60)	23 (68)	
Onset age			0.678
Mean (± SD)	63.66 (7.71)	62.74 (7.59)	
Median (range)	64.50 (53–81)	61 (50–76)	
Antibody, *n* (%)			0.447[a]
Anti-AChR positive	44 (88)	27 (79)	
Anti-MuSK positive	4 (8)	1 (3)	
Seronegative	2 (4)	6 (18)	
Anti-titin antibody[b], *n* (%)			0.149
Positive	35 (71)	16 (50)	
Negative	14 (29)	16 (50)	
Maximum MGFA, *n* (%)			0.505[c]
Class 2	27 (54)	15 (44)	
Class 3, 4	21 (42)	16 (47)	
Class 5	2 (4)	3 (9)	
Thymectomy, *n* (%)	6 (12)	3 (9)	0.918
Treatment options, *n* (%)			0.032[d]
PRED + AZA	35 (70)	15 (44)	
PRED only	9 (18)	13 (38)	
AZA only	6 (12)	6 (18)	

PRED prednisone, *AZA* azathioprine

*Significant at $p<0.05$, univariate analysis (combination of PRED+AZA significantly better by logistic regression analysis)

[a]Anti-AChR positive vs anti-AChR negative (i.e., MuSK positive and seronegative)

[b]81 patients tested for anti-titin antibodies

[c]MGFA Class 2 vs MGFA Classes 3, 4, and 5

[d]PRED+AZA vs PRED only and AZA only

Table 4 Prognostic factors affecting outcome in late-onset (LOMG) at the final follow-up of immunosuppressive treatment

	Favorable prognosis	Unfavorable prognosis	Significance* (*p*)
Number of patients, *n* (%)	53 (63)	31 (37)	
Gender, *n* (%)			0.620
Female	18 (34)	13 (42)	
Male	35 (66)	18 (58)	
Onset age			0.926
Mean (± SD)	63.3 (± 7.21)	63.2 (± 8.43)	
Medium (range)	63 (53–81)	62 (50–78)	
Antibody, *n* (%)			0.852[a]
Anti-AChR positive	44 (83)	27 (87)	
Anti-MuSK positive	5 (9)	0	
Seronegative	4 (8)	4 (13)	
Anti-titin antibody[b], *n* (%)			0.716
Positive	34 (67)	16 (53)	
Negative	17 (33)	14 (47)	
Maximum MGFA, *n* (%)			0.391[c]
Class 2	27 (51)	12 (39)	
Class 3, 4	23 (43)	16 (51)	
Class 5	3 (6)	3 (10)	
Thymectomy, *n* (%)	5 (9)	7 (23)	0.181
Treatment options, *n* (%)			0.299[d]
PRED + AZA	38 (72)	18 (58)	
PRED only	8 (15)	8 (26)	
AZA only	7 (13)	5 (16)	

PRED prednisone, *AZA* azathioprine

*Significant at $p < 0.05$, univariate analysis

[a]Anti-AChR positive vs anti-AChR negative (i.e., MuSK positive and seronegative)

[b]81 patients tested for anti-titin antibodies

[c]MGFA Class 2 vs MGFA Classes 3, 4, and 5

[d]PRED+AZA vs PRED only and AZA only

Comparison of MGFA PIS with MG composite scores at the last visit

Sixty-five patients were evaluated in detail with MG composite scores. MG composite score was ≤ 3 (accepted as mild) in 55 (85%) and > 3 in 10 (15%) patients. In these patients, MGFA PIS was favorable in 45 (65%) and unfavorable in 23 (35%) patients.

Statistical analysis revealed a significant correlation between MGFA PIS and MG Composite score (KAPPA = 0.42, moderate correlation). In the patients with favorable MGFA PIS, 98% had a low MG Composite score, as expected. In those with unfavorable MGFA PIS, 39% had a high MG Composite score, again as expected; however, 61% of these patients had a low score.

Discussion

In this study of 95 patients with non-thymomatous generalized LOMG followed for ≥ 3 years, a high percentage each of men, ocular onset, anti-AChR, and anti-titin ab positivity was found to be similar to that in previous LOMG studies (Table 1) [1–7]. As reported, thyroid disease was the most frequent autoimmune disease in our cohort of LOMG [1, 3]. The most striking difference between the decades was the increasing frequencies of both anti-AChR and anti-titin ab in higher decades. A rising frequency with age of the percentage of anti-AChR ab [7, 20] and anti-titin ab [13] in older patients has been reported.

The effect of immunosuppressive treatment on prognosis was evaluated in 84 generalized LOMG patients followed

for ≥ 3 years. Favorable outcome (MGFA PIS categories of CSR, PR and MM) was seen in 60% of generalized LOMG at the end of 3 years of immunosuppressive treatment, and in 63% at the end of follow-up. When the MGFA PIS category of improved (I) was added, CSR + PR + MM + I was present in 90% at the end of 3 years and 87% at the end of follow-up. Logistic regression analysis revealed the use of PRED + AZA to be a significantly favorable factor at the end of 3 years, but not at the end of follow-up. A study with follow-up of 3 years had concluded that the combination of PRED and AZA was better than the use of each agent alone in MG [21] and the same conclusion was reached in a study with LOMG patients [3]. The superiority of this combination was confirmed in our LOMG cohort.

Anti-titin ab have been reported to be present in about one-third [8] to over one-half [5, 13] of anti-AChR positive LOMG patients. In our cohort, they were positive in close to two thirds of the tested patients with generalized LOMG. The course of MG with anti-titin ab has been variably reported as severe [22] or not [13]. In this study, one-half of the LOMG patients with anti-titin ab had mild disease. Outcome was favorable in about 60% of the LOMG patients with anti-titin ab. Thus, the presence of anti-titin ab was not necessarily a negative factor with regard to either severity or prognosis in this cohort of LOMG.

It was interesting, though perhaps not unexpected, that a significant prognostic factor (use of PRED + AZA) was found at the end of 3 years and the significance of this factor disappeared at the end of follow-up. MG tends to improve after many years [23]; it is possible that the probability of determining prognostic factors is higher at a shorter time period than at the end of follow-up. This observation may be worth considering in planning and evaluating studies in MG.

Our small subgroup of five anti-MuSK positive patients deserves comment. Onset symptoms were bulbar (including one with head drop) in all of the patients. The disease was severe in four of them. Outcome of all of these patients was favorable. This suggests that MuSK MG may be easier to treat in older people.

Another finding in the study was that many patients with mild disease (maximum MGFA Class 2) who received a low maximum dose of PRED (≤ 30 mg/day), usually together with AZA, had a favorable outcome. This finding implies that low-dose PRED with additional AZA may be sufficient in mild disease of older people. It is possible that older people respond better-to-low doses of immunosuppressives, compared to young people [24].

Correlation between MGFA PIS [18] and MG composite scores [19], tested in 65 patients, was almost perfect in those with favorable MGFA PIS score. However, the correlation was not as good in those with unfavorable MGFA PIS score: unexpectedly, close to two thirds of these patients had a low (good) MG composite score. That MGFA PIS score evaluates the status of the patient over a long period requiring stability, while MG composite score estimates the status of the patient at a particular point in time could be one reason for this discrepancy. In conclusion, it can perhaps be said that MG composite scores are helpful in supporting the MGFA PIS score in patients doing well, but they can be deceiving in unstable patients.

This study has limitations foremost because of its retrospective nature. There were patients who could not be reached by phone or letter. In the patients reported to have died, the cause in the majority did not appear to be MG-related; however, it is difficult to be certain of this. It is possible that different conclusions would have been reached with more definite information. This might have influenced our results on the severity and outcome of the disease, but not our results on demographic features and serology.

Our study has several positive aspects. We had a high number of patients, all from one neuromuscular clinic and included without selection. Only a specific subtype of MG (generalized LOMG) was evaluated regarding treatment/prognosis. Attempt was made to contact all generalized LOMG patients and those who came were examined in detail. Serology was almost complete with anti-AChR ab tested in all, anti-MuSK ab in all AChR negative, and anti-titin ab in the majority. Treatment was reviewed in detail and the effect of different modalities of immunosuppressive treatment on outcome was evaluated. Anti-titin ab were evaluated in an unselected cohort of LOMG.

In conclusion, our study confirms previously known information on LOMG. It further supports within a specific MG population the benefit of adding AZA to PRED. The study suggests that the presence of anti-titin ab does not point to either severe disease or unfavorable prognosis in generalized, non-thymomatous LOMG. Likewise, the presence of anti-MuSK ab may not point to unfavorable outcome in older people. Our study, thus, contributes to the investigation of a unique MG subgroup. Prospective studies are needed to understand the full scope of LOMG and its prognosis.

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Author contributions SYC, HD, VY and GSD collected and integrated the data. SYC and FD conceived and designed the study. SYC, YGP, PSO and FD analyzed the data, wrote and reviewed the paper. All authors approved the final version of this paper for publication.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Medical Ethical Committee at the Istanbul Medical Faculty, Istanbul University (no.: 2013/95) and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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