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Late-onset non-thymomatous myasthenia gravis: Comparison with early-onset and very late-onset myasthenia gravis

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Abstract

Objective: To identify the clinical characteristics of patients with myasthenia gravis (MG) according to age at onset. *Methods:* We retrospectively recruited 227 non-thymomatous MG patients with adult onset who had been followed up for more than one year. The patients were classified based on the age of symptom onset as "early-onset MG" (EOMG,18–50 years; N=135), "late-onset MG" (LOMG, 50–64 years; N=53), and "very late-onset MG" (VLOMG, ⩾65 years; N=39). Clinical features and serological findings were compared between these groups. *Results:* LOMG patients showed more frequent ocular MG (55%) and less frequent thymic hyperplasia (9%) compared to EOMG patients (31% and 38%; p=0.006 and p<0.001, respectively), and no female preponderance compared to VLOMG patients (female, 49% vs.77%; p=0.014). However, there were no significant differences between VLOMG and EOMG patients, except for more frequent thymic hyperplasia (p<0.001) in EOMG patients. When analyzing female patients only, less frequent secondary generalization (10%) were additionally found in LOMG patients, compared to EOMG (47%, p= 0.008) and VLOMG (59%, p=0.004) patients. Anti-acetylcholine receptor antibody (HR, 5.48; 95% CI, 1.73–17.37; p=0.004) was independently associated with secondary generalization in female EOMG patients.
Conclusion: Our study suggests that LOMG patients, especially female, were characterized by frequent ocular MG and less frequent secondary generalization, distinguished from EOMG and VLOMG patients. Further large epidemiologic studies in Korea are needed to determine the characteristics of MG patients according to the age at onset and gender.

Key words: Myasthenia gravis, age at onset, late-onset, ocular

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction characterized by fluctuating muscle weakness and fatigability. It comprises a clinically and biologically heterogeneous group that can be classified according to the age at onset, the presence of thymic pathology, and autoantibody profiles. Immunogenetic and environmental associations have also been suggested for different clinical phenotypes.

The incidence of MG has increased over time and MG patients with a late onset constitute a crucial subgroup of the MG population.[1-3] It was previously reported that non-thymomatous late-onset MG shows a male bias, more ocular form, positivity of anti-striated muscle antibodies and anti-acetylcholine receptorantibody (AChR-Ab),

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and typically normal or atrophic thymus.[4,5] However, the cut-off age to differentiate early-onset and late-onset MG is heterogeneous according to studies, although the age threshold could be 50 years old, since thymic hyperplasia becomes rare after 50 years of age.[6] Recent genetic studies in western countries have suggested that patients who experience onset after the age of 60 years represent a "true late-onset" MG subgroup, while those with an age at onset of 41–59 years were an intermediate group with a mixture of early- and late-onset MG genetic risk factors.[7,8] There were also obvious changes in aging-related immune phenotypes in the elderly (after age60 or 65 years)[9], which may partially contribute to increased autoimmunity and it has been suggested that immunopathology of disease that onset later in life differ from those that onset earlier.[10] Although there was no consensus onsingle cut-off ageatonset to differentiate clinical features or pathogenesis of MG, few studies attempted to explore if there are more than two groups classified differently.[11] In the present study, we examined clinical and serologic features, and thymic histoloy in a large sample of non-thymomatous MG patients,classified as early-, late- and very late-onset. Thymomatous MG patients were excluded because they have their own clinical features, mostly generalized form, regardless of onset age. In addition, we focused on the gender bias with regard to age at onset and investigated the effects of onset age on clinical features within the same gender.

METHODS

We retrospectively reviewed the medical records of 393 consecutive MG patients with adult onset (age ⩾18 years), who had been followed up for more than 1 year at Samsung Medical Center in South Korea between January 2001 and December 2014. Collected data included date of birth, sex, age at onset, symptoms at onset, type of MG (ocular vs. generalized), history of myasthenic crisis, AChR-Ab test findings, chest computed tomography (CT) findings, thymus pathology or thymoma, and comorbidities such as diabetes, hypertension, dyslipidemia, and thyroid disease.

In cases of clinically suspicious myasthenia gravis (MG) with typical history and signs of fluctuating muscle weakness, MG was diagnosed with the presence of one of the following parameters: positive serum AChR-Ab, positive pyridostigmine (iv) test, and abnormal decremental responses on a repetitive nerve stimulation test. A positive response to anticholinesterase medication and/or the ice-pack test was also helpful for the diagnosis. We defined "pure ocular onset" as MG with only ocular symptoms at onset for more than 3 month before generalization, whereas "ocular MG" was described as weakness restricted to the ocular muscles during the disease course. Myasthenic crisis was defined as a weakness from MG that is severe enough to require intubation. Thymus pathologies were classified as a normal thymus for age, an atrophied thymus, a hyperplastic thymus, and a thymoma.[12]

One hundred ten (28.0%) patients with thymoma were excluded and 47 (12.0%) and 9 (2.3%) patients were excluded because of neonatal or childhood onset (onset age <19 years) and a lack of AChR-Ab testor chest CT results, respectively. Finally, the total of 227 non-thymomatous MG patients was enrolled in the study. The study was approved by Institutional ReviewBoard of Samsung Medical Center.

Definitions of groups

In an attempt to differentiate patients with "true" late-onset, we further divided the patients with onset after 50 years.We classified non-thymomatous patients into the three groups: the "early-onset MG" (EOMG) group with onset at 18-50 years old, "late-onset MG" (LOMG) group with onset at 50–64 years, and "very late-onset MG" (VLOMG) group with onset at ≥65 years.

Statistical analysis

Categorical variables were compared by the χ^2 test or Fischer exact test and continuous variables were examined using Kruskal-Wallis test and Mann–Whitney *U* test. P values were corrected using Bonferroni's method in cases involving multiple testing. The time to secondary generalization was plotted with a Kaplan-Meier survival curve, and log rank tests were used to establish differences between EOMG, LOMG and VLOMG groups. Cox regression analysis was used to assess factors associated with secondary generalization. Potential confounders, including sex, oral prednisone treatment, other immunosuppressant treatment, AChR-Ab positivity, and thymic hyperplasia were included simultaneously in the models so that the analysis could be adjusted. A p-value <0.05 was considered statistically significant. All data analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

This study included 227 non-thymomatous patients (mean age, 53.9 ± 16.0 years; F:M = 144:83) (Table 1). The median age at onset was 44 years (range, 20–83 years) with a peak for the 30–39-year age group. When we analyzed female and male patients according to the age at onset (Figure 1), there was a tendency towards more female patients than male patients in all age groups except for 5059 and 8084-year age group; in females, there was a bimodal distribution with peaks around the ages of 30 and 65 years and a nadir in the age of 50-54 years.

There were several significant differences in demographics between female and male patients. Female MG patients showed higher frequency of VLOMG (21%) and lower frequency of LOMG (18%) than male patients (VLOMG, 11% and LOMG, 33%). Compared to male patients, the frequencies of thymic hyperplasia (31.3% vs. 16.9%; p = 0.015) and AChR-Ab positivity in generalized MG (87.4% vs. 72.9%; p =0.018) were higher but the use of steroid before generalization was less frequent (34.1% vs. 61.2%; p = 0.003) in female patients.

Early-onset, late-onset, and very late-onset MG

The 227 non-thymomatous MG comprised of 135 EOMG (59.5%), 53 LOMG (23.3%), and 39 VLOMG (17.2%) groups (Table 2). The female to male ratio was lower in the LOMG group compared with the EOMG group (1.0 vs. 1.9; p = 0.084) and VLOMG group (1.0 vs. 3.3; p = 0.014). In addition, the LOMG group showed more ocular MG, compared to the EOMG group (54.7% vs. 31.1%; p = 0.006). The EOMG group

Table 1: Demographic data and clinical characteristics of non-thymomatous MG patients.

N = 227	Total MG	Female MG (N = 144)	Male MG (N = 83)	p value*
Onset age, years	44.0 (20-83)	43.5 (20-83)	46.0 (20-83)	0.508
EOMG/LOMG/VLOMG (%)	135/53/39 (60/23/17)	88/26/30 (61/18/21)	47/27/9 (56/33/11)	**0.038**
Disease duration, years (range)	4.8 (1.0-30.5)	5.1 (1.1-30.5)	4.3 (1.0-26.5)	0.187
Follow-up duration, years	3.5 (1.0-19.7)	3.3 (1.0-19.7)	3.7 (1.0-18.9)	0.954
Thyroid dysfunction (%)	30/213 (13.2)	20/132 (15.2)	10/81 (12.3)	0.568
Anti-TPO or Anti-Tg (+) (%)	42/193 (18.5)	27/117 (23.1)	15/76 (19.7)	0.583
Pure ocular at onset	131 (57.7)	82 (56.9)	49 (59.0)	0.759
Ocular MG	83 (36.6)	49 (34.0)	34 (41.0)	0.319
Bulbar involvement at onset	61 (26.9)	41 (28.5)	20 (24.1)	0.474
Secondary generalization (%)	47/131 (35.9)	33/82 (40.2)	14/49 (28.6)	0.178
Time to generalization, years	0.9 (0.3-8.3)	0.8 (0.3-7.0)	1.1 (0.3-8.3)	0.152
Treatment before generalization				
Steroid	58/131 (44.3)	28/82 (34.1)	30/49 (61.2)	**0.003**
Other immunosuppressive agents†	17/131 (13.0)	8/82 (9.8)	9/49 (18.4)	0.156
Myasthenic crisis (%)	17 (7.5)	14 (9.7)	3 (3.6)	0.092
AChR-Ab (+) (%)	159 (70/0)	106 (73.6)	53 (63.9)	0.122
Ocular MG patients	41/84 (48.8)	23/49 (46.9)	18/35 (51.4)	0.591
Generalized MG patients	118/143 (81.8)	83/95 (87.4)	35/48 (72.9)	**0.018**
Chest CT				
Normal or atrophic thymus	168 (74.0)	99 (68.8)	69 (83.1)	
Thymic hyperplasia	59 (26.0)	45 (31.3)	14 (16.9)	**0.017**

EOMG, early-onset myasthenia gravis; LOMG, late-onset myasthenia gravis; VLOMG, very late-onset myasthenia gravis; anti-TPO, anti-thyroperoxidase; anti-Tg, anti-thyroglobulin; AChR-Ab, anti-acetylcholine receptor antibody; CT, computed tomography

*Between female and male MG patients

†Other immunosuppressants included azathioprine, mycophenolate mofetil, and cyclosporin.

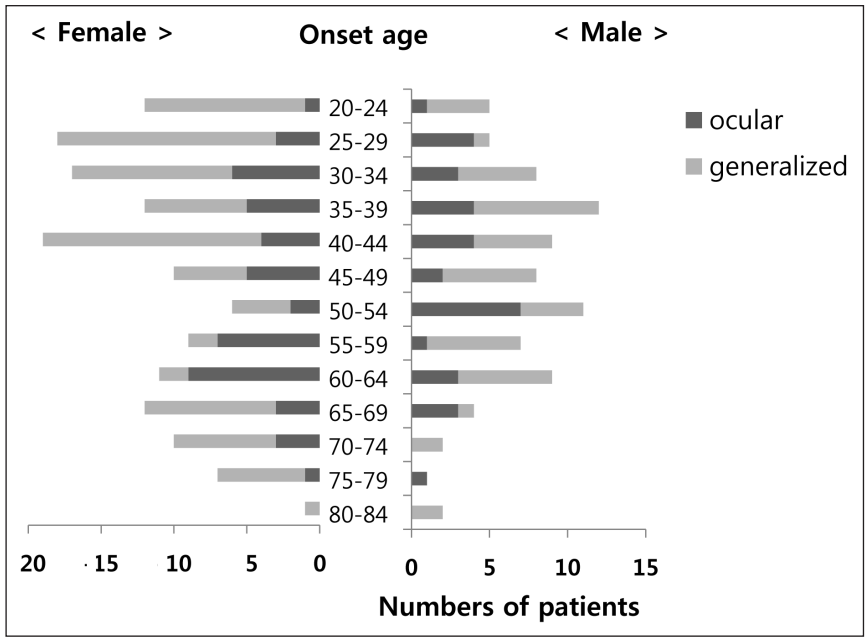

Figure 1: Distribution of ocular and generalized myasthenia gravis (MG) in female and male patients, according to the onset age. The female patients with late-onset myasthenia gravis (LOMG; onset age, 5064 years) had more ocular MG compared to those with early-onset and very late-onset MG.

had more frequent thymic hyperplasia, compared to the LOMG and VLOMG groups (both p <0.001).Cox proportional hazard models revealed that AChR-Ab positivity (HR, 3.08; 95% CI, 1.33–7.11; p= 0.009) and steroid use (HR, 0.05; 95% CI, 0.007–0.36; p = 0.003) were associated with the secondary generalization in the EOMG group. However, there were no significant risk factors for the secondary generalization both in the LOMG and VLOMG groups.

Female MG patients

Female LOMG group showed less frequent secondary generalization (10.0%) and more frequent ocular MG (69.2%) than female EOMG group (46.7% and 27.3%; p = 0.008 and p <0.001, respectively) and female VLOMG (58.8% and 23.3%; p = 0.004 and p = 0.002, respectively; Table 2). However, the time to secondary generalization, the proportion of patients treated with oral prednisone or other immunosuppressants before secondary generalization were not different between three groups. Thymic hyperplasia was more frequently observed in female EOMG group (45.5%) than in female LOMG (11.5%) and female VLOMG (6.7%) groups (p = 0.004 and p <0.001, respectively). There was no significant differences in disease duration, onset symptoms (pure ocular or bulbar), and AChR-Ab positivity between three groups.

The Kaplan-Meier plots of time to secondary generalization revealed that the proportions of female EOMG patients who developed generalized MG, were 27% at 1 year, 40% at 2 years, and 48% at 3 years(N = 12, 95% confidence interval [CI] 14 – 40; N = 17, 95% CI 25 – 55; N = 20, 95% CI 32–64, respectively). In addition, 41%, 54% and 69% of female VLOMG patientsdeveloped generalized MG at 1 year, 2 years and 3 years, respectively (N = 7, 95% CI 17 – 65; N = 9, 95% CI 29 – 78; N = 10, 95% CI 39 – 99, respectively) (Figure 2). However, only 10.0% of female LOMG patients (N = 2) progressed to generalized MG within 6 months after onset and there were no more patients with secondary generalization during the follow-up (median 2.4 years). In log-rank tests, female LOMG patients had less frequent secondary generalization compared to female EOMG and VLOMG patients (p = 0.009 and p = 0.002, respectively).

In female EOMG group, the presence of AChR-Ab (HR, 5.48; 95% CI, 1.73–17.37; p= 0.004) was associated with a higher rate of secondary generalization in Cox proportional hazard model, although the steroid use predicted secondary generalization only in univariate analysis (HR, 0.02; 95% CI, 0.001–0.75; p= 0.035). There were no risk factors for the secondary generalization both in female LOMG and female VLOMG groups.

Table 2: Clinical characteristics of a total MG patients and female MG patients, according to the age at onset

	Total MG (N =227)			Female MG (N =144)		
	EOMG (N = 135)	**LOMG (N = 53)**	**VLOMG (N = 39)**	**Female EOMG (N = 88)**	**Female LOMG (N = 26)**	**Female VLOMG (N = 30)**
Onset age by definition	18–50 years	50–64 years	⩾65 years	<50 years	50–64 years	⩾65 years
Onset age (years)	**35.0 (20-49)**	**57.0 (50-64)**	**70.0 (65-83)**	**33.0 (20-49)**	**58.5 (50-64)**	**70.0 (65-83)**
Female (%)	88 (65.2)	**26 (49.1)†**	**30 (76.9)**	NA	NA	NA
Disease duration (years)	5.2 (1.1-30.5)	4.6 (1.0-22.0)	3.4 (1.0-15.6)	6.1 (1.0-30.5)	5.6 (1.0-20.9)	4.0 (1.5-15.6)
Follow-up duration (years)	3.8 (1.0-19.7)	2.6 (1.0-18.9)	2.8 (1.0-14.0)	3.6 (1.0-19.7)	2.4 (1.0-14.8)	3.0 (1.0-14.0)
Thyroid dysfunction (%)	22/130 (16.9)	3/49 (6.1)	5/34 (14.7)	15/84 (17.9)	1/23 (4.3)	4/25 (16.0)
Anti-TPO or Anti-Tg (+) (%)	31/120 (25.8)	5/43 (11.6)	6/30 (15.4)	19/75 (25.3)	3/20 (15.0)	5/22 (22.7)
Pure ocular at onset	72 (53.3)	36 (67.9)	23 (59.0)	45 (51.1)	20 (76.9)	17 (56.7)
Ocular MG	**42 (31.1)**	**29 (54.7)***	12 (30.8)	**24 (27.3)**	**18 (69.2)**‡**	**7 (23.3)**
Bulbar involvement at onset	41 (30.4)	10 (18.9)	10 (25.6)	28 (31.8)	4 (15.4)	9 (30.0)
Secondary generalization (%)	29/72 (40.3)	7/36 (19.4)	12/23 (52.2)	**21/45 (46.7)**	**2/20 (10.0)*‡**	**10/17 (58.8)**
Time to generalization (years)	1.1 (0.3-8.3)	0.9 (0.4-1.1)	0.8 (0.3-3.0)	0.9 (0.3-7.0)	0.5 (0.4-0.5)	0.7 (0.3-3.0)
Treatment before generalization						
Steroid	30/72 (41.7)	16/36 (44.4)	12/23 (52.2)	14/45 (31.1)	7/20 (35.0)	7/17 (41.2)
Other immunosuppressive agents	8/72 (11.1)	6/36 (16.7)	3/23 (13.0)	5/45 (11.1)	2/20 (10.0)	1/17 (5.9)
Myasthenic crisis (%)	12 (8.9)	2 (3.8)	3 (7.7)	10 (11.4)	1 (3.8)	3 (10.0)
AChR-Ab (+) (%)	99 (73.3)	30 (56.6)	30 (76.9)	69 (78.4)	15 (57.7)	22 (73.3)
Ocular MG patients	21/42 (50.0)	13/29 (44.8)	7/12 (58.3)	12/24 (50.0)	8/18 (44.4)	3/7 (42.9)
Generalized MG patients	78/93 (83.9)	17/24 (70.8)	23/27 (85.2)	57/64 (89.1)	7/8 (87.5)	19/23 (82.6)
Chest CT						
Normal or atrophic thymus	84 (62.2)	48 (90.6)	36 (92.3)	48 (54.5)	23 (88.5)	28 (93.3)
Thymic hyperplasia	**51 (37.8)**	**5 (9.4)****	**3 (7.7)****	**40 (45.5)**	**3 (11.5)***	**2 (6.7)****

EOMG, early-onset myasthenia gravis; LOMG, late-onset myasthenia gravis; VLOMG, very late-onset myasthenia gravis; anti-TPO, anti-thyroperoxidase; anti-Tg, anti-thyroglobulin; AChR-Ab, anti-acetylcholine receptor antibody; CT, computed tomography; NA, not applicable

*p <0.01; **p <0.001when compared to EOMG

†p <0.05; ‡p <0.01 when compared to VLOMG

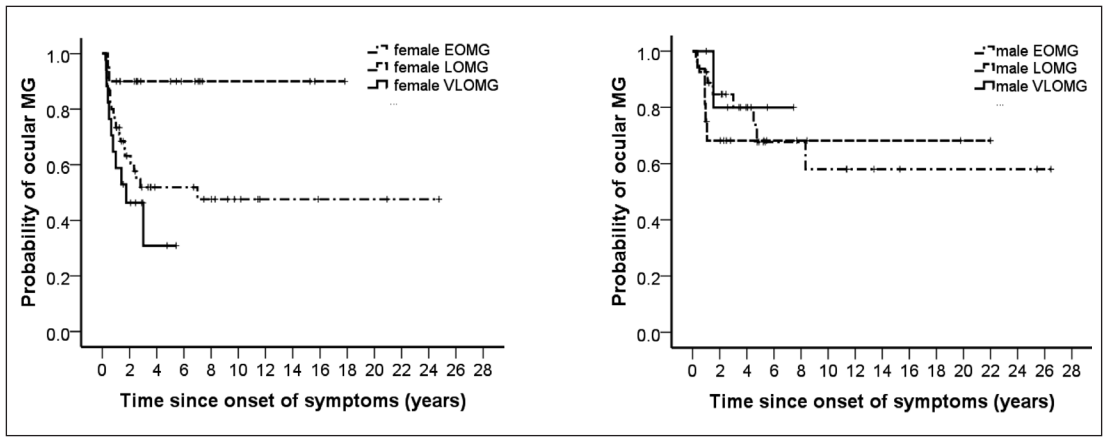

Figure 2. Kaplan-Meier survival plots for disease onset to secondary generalization in female and male patients with EOMG, LOMG, and VLOMG. Log-rank tests were performed.
EOMG, early-onset myasthenia gravis; LOMG, late-onset myasthenia gravis; VLOMG, very late-onset myasthenia gravis

Male MG patients

Thymic hyperplasia was more frequently observed in male EOMG group (23.4%) than male LOMG group (7.4%) and male VLOMG group (11.1%), although statistically not significant. Other clinical features were not different between three groups and there were no significant risk factors for the secondary generalization, in male EOMG, LOMG, and VLOMG groups.

DISCUSSION

We demonstrated that LOMG patients (onset, 50-64 years) were characterized by frequent ocular MG and less frequent thymic hyperplasia compared to EOMG patients. Furthermore, more distinguished features, increased ocular forms and less secondary generalization, were found in female LOMG patients compared to female EOMG and VLOMG patients. Our findings suggested that there could be gender-specificage-related changes in MG risk factors and differentiated treatment approach might be needed to ocular MG patients according to age at onset.

A previous multicenter study for Korean MG in 2006 reported that 40.1% of patients developed MG after 50 years old, although they included those with thymomatous MG.[13] In our hospital-based study, 40.5% of non-thymomatous patients developed MG after the age of 50 and there was a greater increase in the proportion of VLOMG patients (onset age ⩾65 years) from 7% to 22% during a 15-year period (Figure 3). In contrast, the proportion of LOMG patients remained the same. Similar patterns have been described in Canada, in which the incidence of anti-AChR antibody positive MG was increased in the ⩾65 age group, but not in the 45-64 age group.[3] These increasing prevalence of late-onset MG was also previously reported in the epidemiologic studies performed in other countries[2,3,14] and it is believed that MG is currently being diagnosed more often in middle-aged and older individuals than in the past (Table 3).[5,15-17] This trendmay not be simply due to increasing aging population. Environmental or lifestyle changes as well as enhanced diagnosis of MG in the elderly would contribute to this.[3]

Interestingly, LOMG patients were associated witha higher incidence of ocular MG compared to EOMG patients; however, there was no difference in clinical features between VLOMG and EOMG patient except for more thymic

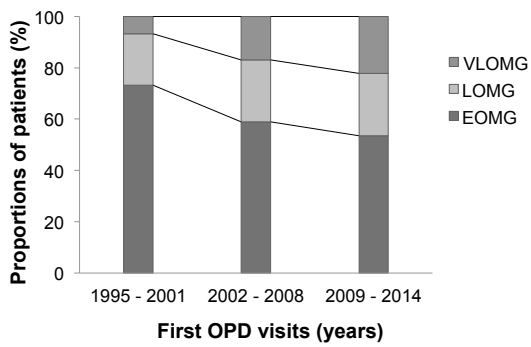

Figure 3. The proportion of non-thymomatous, very late-onset myasthenia gravis (MG) patients (onset age, ⩾65 years) has increased over the past 15 years.
VLOMG, very late-onset MG; LOMG, late-onset MG; EOMG, early-onset MG; OPD, outpatient department

Table 3: Clinical and serologic data for late-onset MG patients from various ethnicities.

Studies	Case N.	Country	Female	Cutoff value of age at onset, years	Oldest Age(range)	Onset symptoms		Ocular MG	AChR-Ab
						Pure ocular	Bulbar		
Donaldson *et al.*[*18]	55	United States	16 (29)	50	NE	18 (33)	NE	6 (11)	39/47 (82)
Slesak *et al.*[*17]	113	Germany	56 (50)	60	60-87	59 (52)	NE	36 (32)	NE
Aguiar *et al.*[*19]	11	Brazil	5 (45)	50	50-74	1 (9)	3 (27)	NE	4/4 (100)
Suzuki *et al.*[5]	83	Japan	48 (58)	50	50-89	NE	19 (23)[†]	37 (45)	53 (64)
Zivkovic *et al.*[11]	114	United States	43 (38)	50	NE	NE	NE	46 (40)	97 (85)
Hellmann *et al.*[*15]	58	Israel	14 (24)	70	70-89	24 (41)	10 (17)	NE	46 (79)
Huang *et al.*[20]	119	China	NS	60	60-84	66 (56)	NE	NE	NE
Murai *et al.*[21]	215	Japan	117 (54)	50	63.8± 9.4[‡]	NE	79 (37)[†]	81 (38)	167 (78)
Evoli *et al.*[*22]	172	Italy	59 (34)	60	61-86	83 (48)	NE	22 (13)	148/162 (91)
Cho *et al.* (Current study)	92[¶]/53[§]/39[ǀ]	South Korea	56 (61)[¶], 26 (49)[§], 30 (77)[ǀ]	50[¶], 50-64[§], 65[ǀ]	50-83	59 (64)	20 (22)	41 (45)	60 (65)

Each item was expressed as numbers (%).
NS, femlae predominance was not significant, although the proportion was not described
NE, not evaluated; AChR-Ab, anti-acetylcholine receptor antibody; MG, myasthenia gravis
*Included patients with thymoma or thymic carcinoma
[†]Bulbar involvement during the disease course; [‡]Expressed as mean ± standard deviation
[¶]LOMG (late-onset MG) + VLOMG (very late-onset MG) with age at onset ⩾50 years; [§]LOMG, age at onset of 50~64 years; [ǀ]VLOMG with age at onset ⩾65 years

hyperplasia in EOMG. There is still no consensus to define late-onset MG and there have also been controversies regarding whether a later onset of symptoms is associated with milder or more severe MG. Previously, several studies reported that patients diagnosed after 50 years old had more bulbar symptoms at onset or high secondary generalization rates than those diagnosed before 50 years old, although these included thymoma-associated and juvenile-onset cases.[18,23] In addition, among non-thymomatous MGpatients with age at onset 60 years or more, 60% of ocular MG showed a progression to generalized disease during follow-up.[24,25] By contrast, recent two studies showed that non-thymomatous late-onset MG patients with onset at age≥50 years had a significantly higher incidence of ocular MG than EOMG patients (38% vs 15%; 45% vs 28%, respectively).[5,11,21] Secondary generalization rate wasalso low in late-onset MG patients with onset after 60 or 70 years in other studies.[17, 26] However, in line with our study, a nationwide survey in Japan revealed that the probability of ocular MG according to onset age showed a U-shaped curve with a dip in the 20-year age group and a skewed deviation towards older age with peaks around 60–64 years.[27] Since so far, there are a few studies about LOMG and VLOMG, these different results could be explained by different ethnicity, methodology, treatment regimens and sample size.

In female MG patients, the incidence rates are low during peri- and early menopause, and begin to rise with aging in our and other studies.[3,28] It is well known that females are predominant in the early-onset form (EOMG) anda male predominance or equal frequency of both sexesis found in LOMG patients as indicated in Table 3.[5,11,17-19,21,22] This reduced female predominance in LOMG may be associated with decreased hormonal effect on immune systems, like in other autoimmune disorders.[15,29] Sex hormones, especially estrogens, might be participate in the pathogenesis of EOMG favoring B-cell mediated immune responses and the development of thymic hyperplasia.[30] However, it is of note that LOMG was also distinguished from VLOMG. Immunosenescence by aging and accumulation of environmental factors could contribute to the increased susceptibility to autoimmunity.[30] The effect of aging on the immune system was observed in other autoimmune disorders such as SLE, where elderly patients had different clinical and serological manifestations and poorer prognosis comparing with young patients.[31] It remains to be further elucidated that less frequent ocular MG compared to LOMGare distinct features of VLOMG.

In addition to the relatively low incidence, female LOMG patients with pure ocular onset had a more benign course with less secondary generalization compared to female EOMG and VLOMG patients. Regarding secondary generalization, several studies have shown that the risk for generalized MG at 2 years was increased in patients with AChR-Ab and that prednisone treatment reduced the incidence of generalized MG.[13,32] A recent study in elderly MG patients (onset age, >70 years) revealed that corticosteroid treatment lowered the risk of generalized MG, although seropositivity for AChR-Ab did not predict the development of generalized MG.[26] In our study, most of ocular onset LOMG patients remained with ocular form (90%) regardless of corticosteroid treatment and/or AChR-Ab seropositivity. There were also no risk factors for secondary generalization in VLOMG, however, due to lack of data about steroid dose and treatment duration, and small samples limited the interpretation of results. The presence of comorbidities such as osteoporosis or diabetes may complicate the corticosteroid treatments in the elderly, although we did not present related data. Larger prospective longitudinal studies could give more detailed information about the relationship between steroid treatment and generalization in late-onset and very late-onset MG patients.

We have several limitations. First, the study was retrospectively performed in a single tertiary hospital. Hence, a possible referral bias cannot be excluded. Second, we did not measure other autoantibodies such as anti-muscle-specific receptor tyrosine kinase or anti-titin/RyR antibodies, which are suggestive of immunologically different mechanisms. Third, we did not include infantile or childhood-onset MG groups, which may consist of mainly ocular MG with a benign course.Finally, the classification of EOMG, LOMG and VLOMG for the sub-analysis may seem arbitrary. Previously, it was reported that the immunological background and genetic basis were distinct between early- and late-onset MG; however, the cut-off value was different between studies (onset ⩾50 or 60 years).[33,34] A recent genetic study suggested the presence of an EOMG/LOMG overlapping group of patients between 40 and 60 years of age[7,8] so the age of 40 and 60 could be the cut-off age of LOMG and VLOMG, respectively. Therefore, the further

studies based on the immunological and genetic factors could help to elucidate the characteristics of EOMG, LOMG and VLOMG groups.

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