

# **A survey of epidemiology, clinical picture, and current treatments for elderly-onset ( $\geq 65$ ) patients with myasthenia gravis in Nagano Prefecture, Japan**

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## **Abstract**

### *Background:*

Our previous population-based study in 1982 – 2001, Nagano Prefecture, Japan, indicated increased numbers of patients with elderly-onset ( $\geq 65$ ) myasthenia gravis (MG).

*Aim:*

We performed a retrospective survey in 2002 – 2012 in the same area, and investigated the epidemiology, clinical picture, and treatments for MG.

*Methods:*

Questionnaires were sent to 23 hospitals and patient records were reviewed. Patients were classified into the non-elderly-onset (15 – 64,  $n = 136$ ) or elderly-onset ( $\geq 65$ ,  $n = 78$ ) group. The questionnaires included details of sex, age/date at onset, initial symptoms, disease severity, association with thymoma, and treatments. Post-intervention status and maximum/maintenance dose of prednisolone were investigated.

*Results:*

The rate of elderly-onset MG patients increased in 2002 – 2012 despite correction for increases in the elderly population. The ratio of MGFA class I was higher, and that of class IIb was lower, and thymectomy rate in non-thymomatous generalized MG patients was lower in the elderly-onset group. There was no marked difference in the rate of intensive treatments (plasma exchange, intravenous immunoglobulin, etc.) between the groups. Immunosuppressive therapies (prednisolone, calcineurin inhibitors) were applied frequently in both groups, while calcineurin inhibitor use rate and mean maximal dose of prednisolone were lower, and the “minimum manifestation status with prednisolone  $\leq 5$  mg” rate was higher in the elderly-onset group.

*Conclusion:*

This study suggested that a low or moderate dose of prednisolone can be fully effective in many elderly-onset MG patients, and some may not require calcineurin inhibitors or thymectomy to reduce prednisolone dose.

## Introduction

Several reports have shown that the incidence of late-onset ( $\geq 50$  years old) myasthenia gravis (MG) has been increasing in American and European countries (1 – 4). Previously, we conducted a population-based epidemiological study on MG from 1982 through 2001 in Nagano Prefecture, Japan, and reported that the incidence of elderly-onset ( $\geq 65$  years old) MG had also increased in Japan (5).

In recent years, MG patients have been treated with several therapies worldwide, including prednisolone, calcineurin inhibitors (CNIs; tacrolimus, cyclosporine), intravenous immunoglobulin (IVIg), and plasma exchange or immune absorption. However, the efficacy of these therapies on elderly-onset ( $\geq 65$  years old) MG patients has not been fully elucidated. Here, we performed a clinical survey of MG from 2002 through 2012 in the same area as in our previous study (5), and investigated the epidemiology, clinical picture, and treatments of elderly-onset MG patients.

## Methods

**Study area.** This study was performed in Nagano Prefecture, situated in the center of Honshu, the main island of Japan. There were 2.13 million inhabitants in Nagano Prefecture in 2012, and age and sex distribution of the population in this prefecture were similar to those of the whole country. However, the ratio of elderly people ( $\geq 65$  years old) was slightly higher than the country as a whole.

**Inclusion criteria.** Questionnaires were sent to 23 hospitals affiliated with Shinshu University School of Medicine that had a department of neurology. Our previous study included a small number of patients that had visited the department of pediatrics, while no pediatric patients were included in the present study.

Therefore, we included only MG patients with age at onset  $\geq 15$  years old (i.e., only adult-onset MG patients).

The neurologists critically reviewed the records of MG patients that had been newly

diagnosed between January 2002 and September 2012. Residents of Nagano Prefecture that had suffered from fluctuating weakness in one or more muscle groups, with a clear positive response to the edrophonium chloride test, and/or elevation of anti-AChR antibody or Musk antibody levels in serum were included in this study. Patients whose onset date was not between 2002 through 2012 were excluded from this study.

The questionnaires were handled carefully using direct mail and a locked computer system for management of data. The profiles of patients, such as name and birth date, were not included on the questionnaires.

**Data analysis and Methods.** The questionnaires included patients' sex, age/date at onset, initial symptoms, disease severity in the most severe state according to the Myasthenia Gravis Foundation of America (MGFA) classification, association with thymoma, and treatments. All patients were classified into the non-elderly-onset group (15 – 64 years old) or the elderly-onset group ( $\geq 65$  years old). In cases

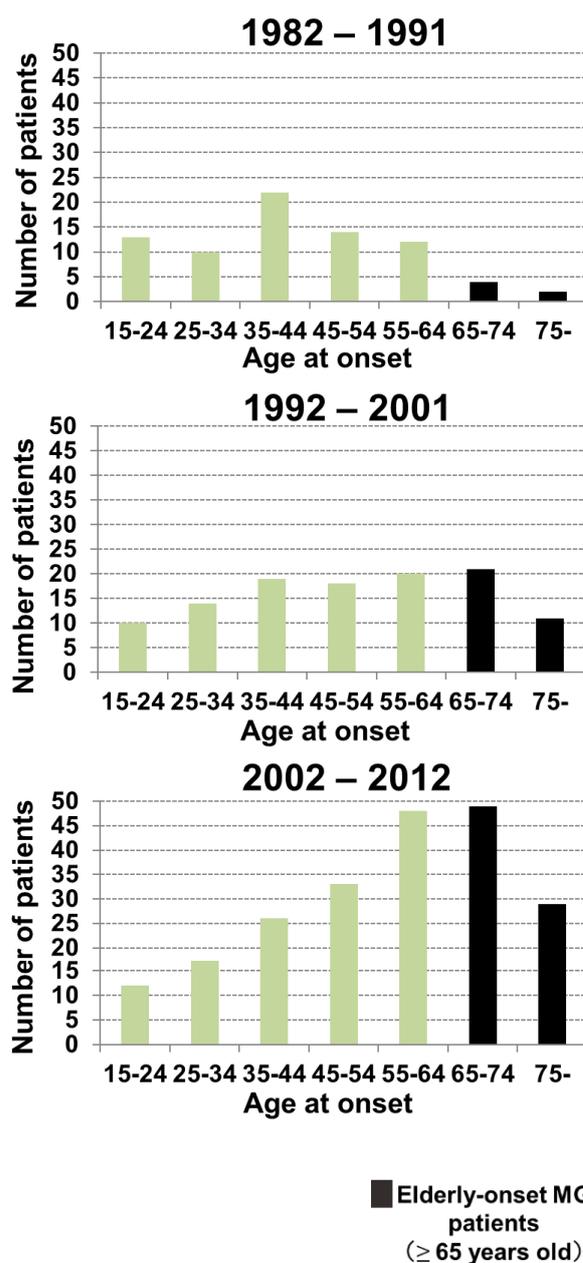
in which the date of onset was uncertain, the age at time of diagnosis was used for classification.

Of the total patients, we reviewed the records of patients that had been treated at Shinshu University School of Medicine (non-elderly-onset;  $n=44$ , elderly-onset;  $n=23$ ) or Aizawa Hospital (non-elderly-onset;  $n = 7$ , elderly-onset;  $n = 6$ ) and checked the MGFA post-intervention status, which was designed to assess the clinical state of MG patients at any time after commencement of treatment (6). We also checked the maximum/maintenance doses of prednisolone as of the end of 2012. In the MGFA post-intervention status (6), Minimum Manifestation (MM) status indicates that “the patient has no symptoms or functional limitations from MG but has some weakness on examination of some muscles.” International consensus guidance for management of MG recommend MM or better with no more than Grade 1 Common Terminology Criteria for Adverse Events (CTCAE) medication side effects (Grade 1; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not

indicated (7)) as the goal of treatment (8). In the multicenter follow up study in Japan (9), multivariate regression revealed that achieving MM or better status with prednisolone  $\leq 5$  mg showed significant positive effects ( $p = 0.008$ ) on QOL (MG-QOL 15 – J (10)). We therefore calculated the percentage of patients that had achieved and maintained “MM with PSL  $\leq 5$  mg” as a treatment target. Appropriate evaluation of side effects is difficult in a multicenter retrospective study, so we did not evaluate the severity of side effects.

Data regarding age at onset and association with thymoma were compared with those of our previous study conducted from 1982 through 2001 (5).

The age at onset is presented as the mean  $\pm$  standard deviation. The chi-squared test was used to evaluate the significance of differences among the terms, and the  $t$  test was used for evaluation of differences between the mean doses of prednisolone. In all analyses,  $P < 0.05$  was taken to indicate statistical significance.



**Figure 1.** The patients were classified according to age at onset per decade. We compared the data with those of our previous study conducted from 1982 through 2001 (5). The percentages of non-elderly-onset and elderly-onset MG patients in 2002 – 2012 were 63.6% and 36.4%, respectively.

**Table 1.** Corrected percentages of elderly-onset MG patients in Nagano Prefecture

Elderly residents ( $\geq 65$ years old)		
In Nagano Prefecture		
		population increase rate
1985	13.6%	= 19.0 / 13.6
1995	19.0%	
2005	23.8%	= 23.8 / 19.0

Elderly-onset MG		
	percentage	Corrected percentage
1982 – 1991 ( $n = 77$ )	7.8% ( $n = 6$ )	
1992 – 2001 ( $n = 113$ )	28.3% ( $n = 32$ )	= 28.3% $\times$ 13.6 / 19.0
2002 – 2012 ( $n = 214$ )	36.4% ( $n = 78$ )	= 36.4% $\times$ 19.0 / 23.8

Using the population of Nagano Prefecture in 1985, 1995, and 2005 as the standard for each decade (data from Japan National Census), we calculated the population increase rate in elderly residents ( $\geq 65$  years old) in Nagano Prefecture and corrected the percentages of elderly-onset MG patients per decade.

## Results

We received responses to the questionnaire from

19 hospitals (82.6%), and 13 of these had a total of 214 newly diagnosed MG patients (non-elderly-onset;  $n = 136$ , elderly-onset;  $n = 78$ ) that had developed MG between 2002 and 2012. In all of the patients, serum anti-AChR antibody was determined by commercial laboratories, and positive results were detected in 181 patients (84.6%). The Anti-AChR antibody positive ratios were not markedly different between the two groups in the present study; 83.1% (113 of 136 patients) in the non-elderly-onset group and 87.2% (68 of 78 patients) in the elderly-onset group. One patient had elevated serum Musk antibody level.

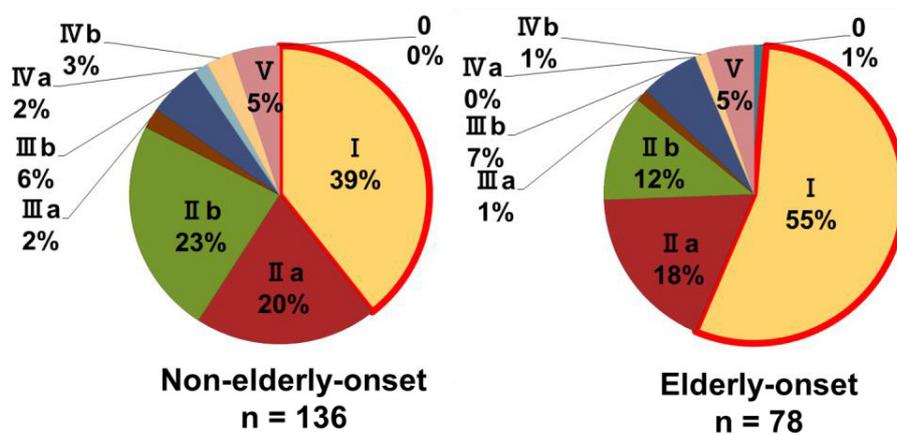
**Age at onset and sex ratio.** The patients were classified according to age at onset per decade, and the numbers of patients were indicated as bar graphs: 1982 – 1991, 1992 – 2001, 2002 – 2012 (Figure 1). We compared the data with those of our previous study conducted from 1982 through 2001 (5).

The percentages of non-elderly-onset and elderly-onset MG patients in 2002 – 2012 were 63.6% and 36.4%, respectively. The oldest age at

**Table 2.** Numbers/percentages of patients classified according to initial symptoms

		Non-elderly-onset (n = 136)		Elderly-onset (n = 78)		P-value
		Total patients	%	Total patients	%	
Initial symptoms	ptosis	111	82%	70	90%	0.54
	diplopia	85	63%	40	51%	0.26
	muscle weakness of the limbs	65	47%	14	18%	< 0.001
	bulbar symptoms	47	34%	19	24%	0.19

A gross number of each symptom is written in each section.



**Figure 2.** Percentages of patients were classified according to MGFA classification. The percentage of class I patients was higher, and that of class IIb patients was lower in the elderly-onset group than in the non-elderly-onset group.

onset was 85 years old and the youngest was 16 years old. The percentages of elderly-onset MG patients in each decade, including the data from our previous study (5), were as follows: 7.8% in 1982 – 1991; 28.3% in 1992 – 2001; and 36.4% in 2002 – 2012 (Table 1). Using the populations of Nagano Prefecture in 1985, 1995, and 2005 as

the standard for each decade, we calculated the population increase rate of residents  $\geq 65$  years old in Nagano Prefecture, and used this rate to correct the percentage of elderly-onset MG patients. For example, the percentages of residents  $\geq 65$  years old in 1985 and 1995 were 13.6% and 19.0%, respectively (Table 1, data

from Japan National Census), yielding a population increase rate of 13.6/19.0. The corrected percentage of elderly-onset MG patients in 1992 – 2001 was calculated as 28.3%  $\times$  13.6/19.0 = 20.3%. The corrected percentages were as follows: 20.3% in 1992 – 2001 and 29.1% in 2002 – 2012 (Table 1).

There was no difference in the percentage of male/female patients; the percentages of female patients were 53% (72 of 136 patients) in the non-elderly-onset group and 53% (42 of 78 patients) in the elderly-onset group.

**Initial symptoms.** The numbers and percentages of patients were classified according to their initial symptoms (Table 2). The percentages of patients with ocular symptoms (ptosis and diplopia) were high in both non-elderly-onset and elderly-onset groups: ptosis, 82% and 90%; diplopia, 63% and 51%. The percentages of bulbar symptoms were 34% and 24%. The number of patients with muscle weakness of the limbs was significantly lower in the elderly-onset group compared to the non-elderly-onset group (18% vs. 47%, respectively,  $P < 0.001$ ).

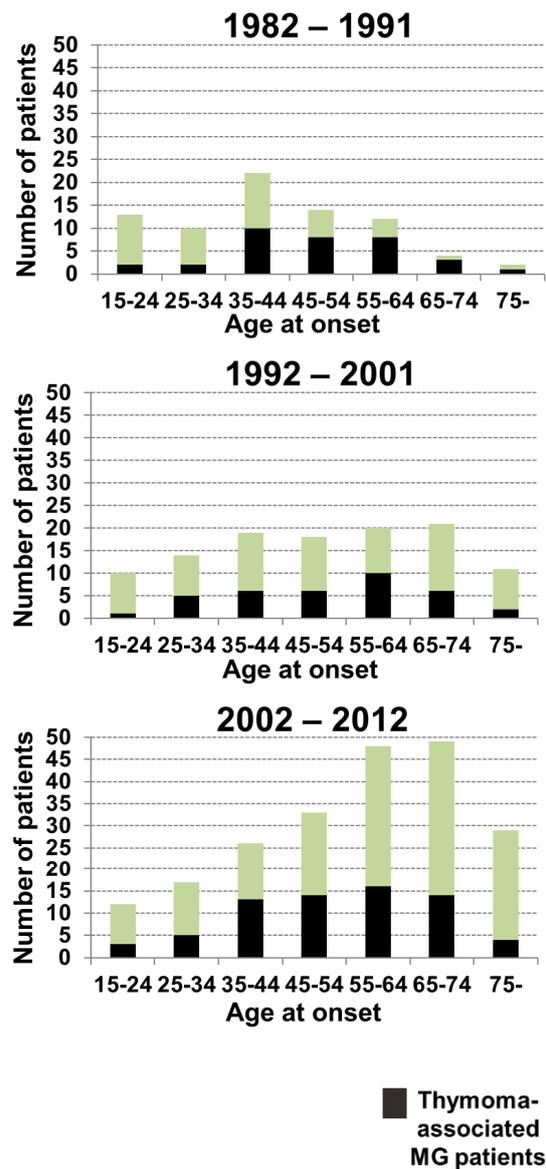
**MGFA classification.** The percentages of patients were classified according to MGFA classification corresponding to the most severe stage (Figure 2). The percentage of class I patients was higher and that of class IIb patients was lower in the elderly-onset group than the non-elderly-onset group (I ; 55% vs. 39%, IIb; 12% vs. 23%, respectively,  $P = 0.106, 0.044$ ).

**Thymoma-associated MG** Thymoma-associated MG patients were also indicated as bar graphs classified according to age at onset per decade (Figure 3; also compared with the data of our previous study (5)). Patients for whom it was not known whether thymectomy had been conducted were excluded. The thymoma ratios in “total MG” per decade were 44.2% in 1982 – 1991, 31.9% in 1992 – 2002, and 32.2% in 2002 – 2012. The corresponding values in “the non-elderly-onset” group were 42.3% in 1982 – 1991, 34.6% in 1992 – 2002, and 37.5% in 2002 – 2012. Those in “the elderly-onset” group were 66.7% in 1982 – 1991, 25.0% in 1992 – 2002, and 23.1% in 2002 – 2012.

**Treatments.** All MG patients with thymoma

underwent thymectomy. The thymectomy ratio in “non-thymomatous” generalized MG patients in the elderly-onset group was lower than that in the non-elderly-onset group (16 patients, 25.8% vs. 35 patients, 41.2%, respectively).

The numbers of patients that had been treated with IVIg, plasma exchange, or immune absorption were small in both groups, and the ratios of these therapies were not significantly different between the two groups: non-elderly, 26 patients (17.0%) vs. elderly, 14 patients (17.9%). The percentages of oral medications (ChE inhibitor alone, prednisolone, prednisolone + CNIs) in each group are shown in Figure 4. Immunosuppressive therapies (prednisolone, CNIs) were frequently administered in both groups: non-elderly, 67%; elderly, 65%. There was no difference in the rate of prednisolone use between the two groups, but more patients had been treated with the combination of prednisolone and CNIs in the non-elderly-onset group than in the elderly-onset group (42% vs. 23%, respectively). The mean maximal dose of prednisolone was lower in the elderly-onset



**Figure 3.** Thymoma-associated MG patients are indicated as bar graphs classified according to age at onset per decade. In 1992 – 2002 and 2002 – 2012, thymoma ratio in the total MG/non-elderly/elderly groups were about 32%/35%/25%, consistent with the results of the national survey in Japan (11). These observations suggested that thymoma ratio had not changed significantly in these 20 years. The number of patients during 1982 – 1991 was small, so the data in this decade may lack reliability.

group than in the non-elderly-onset group ( $20.89 \pm 15.37$  mg vs.  $26.54 \pm 15.49$  mg, respectively,  $P = 0.0412$ ) (Table 3). Moreover, the percentage of patients that achieved and maintained MM with  $PSL \leq 5$  mg was higher in the elderly-onset group than in the non-elderly-onset group (68.2% vs. 60.3%, respectively,  $P = 0.481$ ) (Table 3).

## Discussion

The corrected percentages suggested that the rate of elderly-onset MG patients increased over the past 30 years despite correction for increases in the elderly population (Table 1). This may have been due to increased visibility of elderly-onset MG and widespread measurement of anti-AChR antibodies.

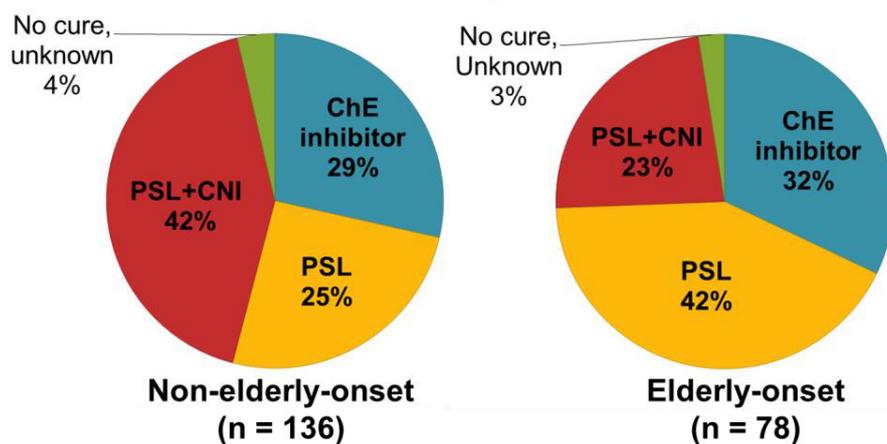
In the national survey of MG in Japan, 2006 (11), the ratios of elderly-onset patients ( $\geq 65$ ) in adult-onset MG ( $\geq 15$ ) were about 9.0% in 1987 and 19.2% in 2006, which were slightly lower than those in the present study. This may have been because the percentage of elderly people ( $\geq$

65 years old) in Nagano Prefecture was 3% – 5% higher than that in the whole country during this 30-year period (data from Japan National Census).

**Table 3.** Mean maximal doses of prednisolone, and percentages of patients achieving MM\* with  $PSL \leq 5$  mg

	Non-elderly -onset ( <i>n</i> = 51)	Elderly -onset ( <i>n</i> = 29)	<i>P</i> -value
Mean maximal doses of Prednisolone	26.54 mg	20.89 mg	0.0412
Achieved MM* or better status with $PSL \leq 5$ mg (%)	60.3%	68.2%	0.481

\*Minimum manifestation status: no symptoms of functional limitations from MG but slight weakness of some muscles (6). Of the total patients, we reviewed the records of patients that had been treated at Shinshu University School of Medicine (non-elderly-onset;  $n=44$ , elderly-onset;  $n=23$ ) or Aizawa Hospital (non-elderly-onset;  $n=7$ , elderly-onset;  $n=6$ ) and checked the MGFA post-intervention status (6) and the maximum/maintenance doses of prednisolone as of the end of 2012.



**Figure 4.** Percentages of oral medications (ChE inhibitor alone, prednisolone, CNIs; tacrolimus, cyclosporine. Only one patient in each group had cyclosporine, and others had tacrolimus in the present study). Immunosuppressive therapies (prednisolone and/or CNIs) were frequently administered in both groups. More patients had been treated with the combination of prednisolone and CNIs in the non-elderly-onset group.

The national survey in Japan, 2006, indicated a sex ratio of all patients with MG (male: female) of 1:1.7 (11). Some previous reports indicated that males exceed females in cases with middle-age or older onset; e.g., Male: Female = 1.1:1 in MG with onset at  $\geq 40$  years old (12) and 1.9:1 in MG with onset at  $\geq 60$  years old (13). The lack of difference in sex ratio in this study was probably due to exclusion of patients with childhood-onset (0 – 14 years old) and the inclusion of more patients with onset in middle age or older.

In the present study, 90% of elderly-onset MG

patients had ocular symptoms, while limb weakness at time of diagnosis was significantly lower and the percentage of MGFA class I patients was higher in the elderly-onset group. Also, the percentage of MGFA class IIb patients was lower in the elderly-onset group. This study suggested that the vast majority of elderly-onset MG patients were mainly suffered from ocular symptoms, not being associated with severe limb weakness or bulbar symptoms.

The national survey in Japan, 2006, indicated that thymoma ratio in MG had increased from 21.1% in 1987 to 33.8% in 2006 (11). In 1992 –

2002 or 2002 – 2012, the thymoma ratios in the total MG/non-elderly (15 – 64 years old)/elderly ( $\geq 65$  years old) groups were about 32%/35%/25%, which were consistent with the results of the national survey, suggesting that thymoma ratio had not changed significantly over this 20-year period. The number of patients during 1982 – 1991 was small, so thymoma ratio in this group is not significantly referable.

A randomized controlled study (MGTX) (14) indicated that thymectomy plus prednisolone improved clinical outcomes compared to prednisolone alone over a 3-year period, and that thymectomy lowered the required prednisolone dose. In addition, it indicated that thymectomy can also be conducted safely in non-thymomatous general MG patients. Thus, surgery may be recommended in non-thymomatous general MG patients; however, efficacy and safety of surgery on elderly-onset MG patients has not been established. In the present study, the thymectomy ratio in non-thymomatous generalized MG patients in the elderly-onset group was lower than that in the non-elderly-onset group. This might be due to the

avoidance for operation risk and to sufficient therapeutic effects obtained by oral medications.

Very few studies evaluated the efficacies of immunosuppressive therapies in large numbers of cases of elderly-onset MG. In this study, immunosuppressive therapies (prednisolone, CNIs) were administered frequently in both groups. In the elderly-onset group, the rate of CNI use and the mean maximal dose of prednisolone and thymectomy ratio in the non-thymomatous general MG patients were lower, and the ratio of MM with PSL  $\leq 5$  mg was higher, suggesting that a low or moderate dose of prednisolone can be fully effective in many elderly-onset MG patients and some did not require thymectomy or CNIs to reduce the dose of prednisolone. This therapeutic tendency might be explainable by mild clinical picture of the elderly-onset MG patients.

It has been suggested that intensive treatments on initial treatment or re-exacerbation (steroid pulse, plasma exchange, immune absorption, IVIg) can also be conducted in elderly-onset MG patients (13). Since indication and outcome of these therapies in elderly-onset MG patients have

not been fully elucidated, the therapeutic options for these intensive treatments are supposed to be less frequent comparing to non elderly-onset MG patients. In the present study, however, the administration ratios of these therapies were not markedly different between the two groups, which might be due to the relatively small number of patients receiving these therapies.

Although pyridostigmine should be part of the initial treatment in most patients with MG, its effect is still speculative so we did not estimate its use rate or efficacy in this study.

In conclusion, the incidence of elderly-onset MG patients has been increasing over the past 30 years. There were differences in clinical pictures and responses to treatment between elderly-onset and non-elderly-onset MG patients. This study suggested that a low or moderate dose of prednisolone can be fully effective in many elderly-onset MG patients and that some do not require thymectomy or CNIs to reduce the dose of prednisolone.

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