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Clinical features and treatment status of adult myasthenia gravis in Japan

Hiroyuki Murai,[1] Masayuki Masuda,[2] Kimiaki Utsugisawa,[3] Yuriko Nagane,[3] Shigeaki Suzuki,[4] Tomihiro Imai,[5] Masakatsu Motomura,[6] Shingo Konno[7] and Jun-ichi Kira[1]

[1]Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Department of Neurology, Tokyo Medical University, Tokyo, Japan, [3]Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan, [4]Department of Neurology, Keio University School of Medicine, Tokyo, Japan, [5]Department of Occupational Therapy, Sapporo Medical University School of Health Sciences, Sapporo, Japan, [6]Department of Clinical Neuroscience and Neurology, Nagasaki University Hospital, Nagasaki, Japan, [7]Department of Neurology, Toho University Medical Center Ohashi Hospital, Tokyo, Japan

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Correspondence
Hiroyuki Murai, MD, PhD, Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
Tel: +81-92-642-5340
Fax: +81-92-642-5352
Email: hmurai@neuro.med.kyushu-u.ac.jp

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Abstract

Objective Myasthenia gravis (MG) is classified as early-onset MG (EOMG; age at onset ≤49 years), late-onset MG (LOMG; age at onset ≥50 years) or thymoma-associated MG (TAMG) (E-L-T classification). To clarify the characteristics of each group in the E-L-T classification in Japan, we carried out multicenter analyses of MG.

Methods A total of 640 adult patients from 11 MG centers participated in the study. Age at onset, sex, clinical symptoms, frequency of crisis, thymic pathology, positivity of autoantibodies against acetylcholine receptor (AChR) and muscle-specific receptor tyrosine kinase (MuSK), selected treatment, Cushingoid appearance and post-intervention status were evaluated in each group.

Results EOMG, LOMG and TAMG accounted for 44%, 33%, and 23% of the patients, respectively. Females predominated in the EOMG group (77%), whereas there was no sex difference in the LOMG group. The frequency of ocular MG was the highest in the LOMG group (EOMG 15%, LOMG 38%, TAMG 12%). Bulbar symptoms and crisis were most frequent in the TAMG group. Anti-AChR antibody was always positive in patients with TAMG (EOMG 70%, LOMG 78%, TAMG 99%), whereas anti-MuSK antibody was never positive in TAMG patients, and more frequently detected in EOMG patients than in LOMG patients. Thymectomy was carried out in 51% of EOMG patients, 26% of LOMG patients and 97% of TAMG patients. Immunotherapy was carried out most aggressively in TAMG patients, and least aggressively in LOMG patients. Minimal manifestations or better with prednisolone ≤5 mg were achieved only in one-third of EOMG and TAMG patients.

Conclusion Thymoma-associated MG required the most aggressive immunotherapy, followed by early-onset MG. (Clin. Exp. Neuroimmunol doi: 10.1111/cen3.12091, January 2014)

Introduction

Myasthenia gravis (MG) is a common autoimmune disease affecting the neuromuscular system. MG patients produce autoantibodies against molecules in neuromuscular junctions, such as the acetylcholine receptor (AChR),[1] muscle-specific receptor tyrosine kinase (MuSK)[2,3] and low-density lipoprotein receptor-related protein 4 (Lrp4).[4] MG is a heterogeneous disease clinically, histologically and autoimmunologically. Clinically, ocular myasthenia is a unique category, distinguished from the generalized form. Thymic histology divides patients into thymoma-associated MG (TAMG) and non-thymomatous MG.

Autoimmunologically, patients are designated as seronegative MG if the aforementioned antibodies are all negative. Age at onset is another important factor. Early-onset MG (EOMG) has different characteristics from late-onset MG (LOMG). Infantile- and child-onset MG, which is common in eastern Asia,[5] is also a distinct group.

Therefore, to evaluate the results of a large-scale clinical study or epidemiological survey, proper classification is mandatory. In the literature, MG is divided into EAMG and LOMG. However, there is no consensus on these definitions, with age thresholds of 40,[6,7] 50[5,8–13] or 60 years[14–16] in use, and various inclusion criteria for TAMG. We propose that TAMG should be separated, because this group is clinically distinct and has an aspect of paraneoplastic syndrome.[12] In addition, we consider the most appropriate age threshold for distinction between EOMG and LOMG to be 50 years based on the pathological findings that thymic hyperplasia becomes rare after 50 years.[17] In the present study, MG patients were classified into EOMG with age at onset ≤49 years, LOMG with age at onset ≥50 years and TAMG (E-L-T classification).

We carried out a nationwide epidemiological survey in 2006 elucidating the prevalence and onset age-related characteristics of MG in Japan.[5] However, there were some limitations to that study. First, treatment status was not thoroughly evaluated. Second, anti-MuSK antibodies were rarely measured at the time of study. Third, the response rate was quite low (36.9%), resulting in a high rate of TAMG (32.0%). We herein describe the results of detailed retrospective multicenter analyses of MG in 2012 to evaluate the clinical and treatment status of MG in Japan using the E-L-T classification.

Methods

Patients

The study was carried out by the Japan MG Registry (JAMG-R). The JAMG-R consists of 11 neurological centers in Japan: Hanamaki General Hospital, Keio University Hospital, Iizuka Hospital, Sapporo Medical University Hospital, Saitama Medical Center, Tokyo Medical University Hospital, Toho University Medical Center Ohashi Hospital, National Hospital Organization Sendai Medical Center, Tohoku University Hospital, Nagasaki University Hospital and National Hospital Organization Nagasaki Kawatana Medical Center. The study was approved by the ethics committees of all of the participating institutions.

Consecutive MG patients at various stages of disease, seen in these 11 centers between April and July 2012, were enrolled in the study. Among 676 patients enrolled, 36 patients who did not complete the questionnaire consisting of a self-appraisal scoring system or who did not provide informed consent were excluded from the study. A total of 640 patients were analyzed.

Data collection and analyses

Collected basic information from MG patients included age at onset, sex, MG Foundation of America (MGFA) classification,[18] quantitative MG (QMG) score,[18] MG Composite,[19] MG-activities of daily living (ADL) score,[20] the Japanese version of the 15-item quality of life (QOL) scale (MG-QOL15-J),[21] presence of pure ocular myasthenia (symptoms confined to ptosis or diplopia for more than 2 years), history of bulbar symptoms and crisis, and positivity for anti-AChR and anti-MuSK antibodies. Treatment-related information included MGFA post-intervention status,[18] history of thymectomy, thymic histology, current prednisolone (PSL) dose, maximum PSL dose, latest 1-year dose of PSL, total administration period of PSL, period taking ≥10 mg PSL, period taking ≥20 mg PSL, use of calcineurin inhibitors (CNI), plasma exchange/plasmapheresis and intravenous immunoglobulin (IVIg). We also analyzed the Cushingoid appearance index[22] to evaluate the side-effects of corticosteroids.

We divided the patients into three groups (EOMG, age at onset ≤49 years without thymoma; LOMG, age at onset ≥50 years without thymoma) or (TAMG, thymoma-associated MG; E-L-T classification) and compared these variables. We also compared these variables among ocular and generalized MG patients.

Statistical analysis

To compare the clinical features and treatment status of each group in the E-L-T classification, the Mann–Whitney *U*-test was used for continuous variables and the χ^2-test was applied for categorical variables. Uncorrelated *P*-values were corrected by multiplying them by the number of comparisons. Differences between ocular and generalized MG were tested for significance by the χ^2-test. In all assays, *P*-values <0.05 were considered statistically significant.

Results

Overall clinical status of MG patients in Japan

The overall clinical status of 640 MG patients in Japan as shown by a cross-sectional study is

described elsewhere.[22] Briefly, age at onset was 47.1 ± 18.3 years, and age at present was 57.6 ± 16.5 years, with 66.3% female participants. MGFA classifications were: I, *n* = 151 (23.6%); II, *n* = 255 (39.8%); III, *n* = 138 (21.6%); IV, *n* = 38 (5.9%); and V, *n* = 58 (9.1%). Current severity/QOL scores were: QMG score, 7.0 ± 5.2; MG Composite score, 5.2 ± 6.1; and MG-QOL15-J score, 13.8 ± 12.6. QMG score at time of worst condition was 13.1 ± 6.8. Thymoma was observed in 22.7% of patients. Pure ocular myasthenia comprised 22.0% of total cases. Anti-AChR antibody positivity was 79.2%, and anti-MuSK antibody was positive in 9.8% of anti-AChR antibody-negative patients. Referring to treatment status, thymectomy was carried out in 51.3% of patients, whereas calcineurin inhibitors were used in 48.8%. The current dose of PSL was 4.4 ± 5.9 mg/day, and the total dose of PSL during the last year was 1789.2 ± 1946.5 mg. MGFA post-intervention statuses were as follows: complete stable remission (CSR), *n* = 36 (5.6%); pharmacological remission (PR), *n* = 62 (9.7%); minimal manifestations (MM), *n* = 227 (35.5%); improved (I), *n* = 228 (35.6%); unchanged (U), *n* = 71 (11.1%); worsened (W), *n* = 9 (1.4%); and exacerbated (E), *n* = 7 (1.1%).

Demographic features of each group in the E-L-T classification

The demographic features and clinical characteristics of each group in the E-L-T classification are shown in Table 1. The 640 patients were divided into EOMG (*n* = 280, 43.8%), LOMG (*n* = 215, 33.6%) and TAMG (*n* = 145, 22.7%). Females predominated in the EOMG group (77.3%) and in the TAMG group (63.1%), but there was no sex difference in the LOMG group (54.4%). Disease duration was significantly shorter in LOMG compared with EOMG and

Table 1 Clinical characteristics of myasthenia gravis patients according to the E-L-T classification

	Total *n* = 640	EOMG *n* = 280	LOMG = 215	TAMG = 145	*P*-value
Basic information					
Age at present	57.6 ± 16.5	45.3 ± 13.1	70.5 ± 9.2	60.7 ± 13.5	<0.0001
Female percentage	66.3%	77.3%	54.4%	63.1%	<0.0001†, 0.006‡
Disease duration	10.5 ± 9.8	13.9 ± 11.8	6.5 ± 0.6	10.8 ± 0.8	<0.0001†,§
Age at onset	47.1 ± 18.3	31.3 ± 11.6	63.8 ± 9.4	50.1 ± 12.6	<0.0001
Clinical symptoms, %					
Pure ocular	22.0	15.1	37.8	12.1	<0.0001†,§
Bulbar sign	49.8	51.9	36.6	72.1	<0.0001‡,§, 0.003†
Crisis	10.1	6.1	6.5	23.6	<0.0001‡§
Severity/QOL scales					
QMG score	7.0 ± 5.2	7.6 ± 5.7	6.0 ± 4.4	7.5 ± 5.0	0.006‡, 0.012§
MG Composite	5.2 ± 6.1	5.9 ± 6.8	3.9 ± 4.8	5.9 ± 6.2	0.012†, 0.009§
MG-ADL scale	3.1 ± 3.2	3.4 ± 3.5	2.5 ± 2.7	3.2 ± 3.1	0.009‡
MG-QOL15-J	13.8 ± 12.6	14.3 ± 13.2	12.0 ± 11.6	14.9 ± 12.4	NS
Autoantibodies, %					
Anti-AChR Ab	79.2	70.1	77.9	99.3	<0.0001‡,§
Anti-MuSK Ab*	9.8	12.1	6.3	0.0	<0.0001‡,§
Thymus, %					
Thymectomy	51.3	50.7	25.8	97.2	<0.0001
Thymoma	22.7	0.0	0.0	100	<0.0001
Hyperplasia	55.4	66.9	25.9	0.0	<0.0001
Involuted thymus	44.6	33.1	74.1	0.0	<0.0001
MGFA classification, %					
I	23.6	16.1	37.9	12.8	<0.0001
II	39.8	45.4	38.4	27.7	
III	21.6	24.3	13.7	29.1	
IV	5.9	6.1	3.2	9.9	
V	9.1	6.4	5.0	20.6	

Ab, antibody, ADL, activities of daily living; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific receptor tyrosine kinase; NS, not significant; QMG, quantitative myasthenia gravis; QOL25-J, Japanese version of the 15-item quality of life scale.

*Percentage among anti-acetylcholine receptor (AChR) antibody negative patients.

†Comparison between early-onset myasthenia gravis (EOMG) and late-onset myasthenia gravis (LOMG).

‡Comparison between EOMG and thymoma-associated myasthenia gravis (TAMG).

§Comparison between LOMG and TAMG.

TAMG. Age at onset of TAMG was 50.1 ± 12.6 years, in accordance with the previous nationwide survey in 2006. The pure ocular form accounted for 22.0% of patients in total; however, among the three groups in the E-L-T classification, the LOMG group showed a remarkably high percentage of pure ocular form (37.8%). Bulbar symptoms occurred in approximately half of all MG patients. In particular, a very high incidence of bulbar symptoms was observed in the TAMG group (72.1%). Crisis was also more frequent in the TAMG group (23.6%) compared with the EOMG (6.1%) and LOMG (6.5%) groups.

Severity of disease was evaluated using QMG and MG Composite scores and the MG-ADL scale. LOMG patients showed significantly lower scores on all scales, showing a less severe condition in this group compared with the other two groups. Similarly, the MG-QOL15-J score was the lowest in the LOMG group, but the differences between the score in that group and those in the other two groups did not reach significance. MGFA classification also showed that the TAMG group contained a higher percentage of patients with a severe disease state compared with the EOMG and LOMG groups.

Anti-AChR antibody was almost always positive in the TAMG group. In non-thymomatous MG patients, anti-AChR antibody positivity was higher in LOMG patients than in EOMG patients. In contrast, anti-MuSK antibody was never positive in TAMG patients. In non-thymomatous MG patients, anti-MuSK antibody positivity was higher in EOMG patients than in LOMG patients (among 132 anti-AChR antibody negative patients, anti-MuSK antibody was measured in 81 cases).

Thymectomy had been carried out in approximately half of the MG patients. Nearly all of the thymoma cases received thymectomy (97.2%). In non-thymomatous patients, thymectomy was carried out in 50.7% of EOMG patients and 25.8% of LOMG patients. Histology of thymus show that, in EOMG patients, thymic hyperplasia was frequent (66.9%) and an involuted thymus was uncommon (33.1%); whereas, in contrast, in LOMG patients, hyperplasia was infrequent (25.9%) and an involuted thymus predominated (74.1%). The term hyperplasia was assigned if the germinal center was observed in the thymus pathologically, regardless of number.

Prednisolone administration

The status of PSL administration in each group in the E-L-T classification is summarized in Table 2. Both the current PSL dose and the total dose during the last year were highest in TAMG patients, followed by EOMG patients and lowest in LOMG patients, with statistical significance between TAMG and LOMG patients. This ranking was more evident for maximum PSL dose (TAMG 34.3 mg > EOMG 27.9 mg > LOMG 21.9 mg) with significance in all combinations. Total administration period of PSL, period with a dose of ≥20 mg/day and period with a dose of ≥10 mg were analyzed, and all of these were significantly shorter in LOMG patients than in the patients in the other groups, whereas there was no significant difference between TAMG and LOMG patients (Table 2, Fig. 1).

Immunotherapies

Calcineurin inhibitors were used in 59.6% of patients in the TAMG group, which was higher than the percentage in the non-thymomatous group (EOMG 47.1%, LOMG 47.0%). Plasma exchange and/or plasmapheresis were carried out in 43.6% of TAMG patients, 28.7% of EOMG patients and 21.7% of LOMG patients, being significantly higher in TAMG patients compared with EOMG and LOMG patients. Similarly, IVIg was selected in 14.9% of TAMG patients, which was the highest percentage among the three groups.

MGFA post-intervention status

MGFA post-intervention status is listed in Table 2. There were no statistical differences between groups in terms of CSR and PR. LOMG patients achieved MM status more frequently than did EOMG and TAMG patients. MM or better status with ≤5 mg PSL[21,22] was achieved by 53.9% of LOMG patients, but just 38.1% and 39.0% of EOMG and TAMG patients, respectively.

Cushingoid appearance

Cushingoid appearance was graded from 0 to 3 as follows: 0, no change in appearance; 1, slight appearance change within self-recognizable level (not pointed out by others); 2, moderate appearance changes recognizable also by others (sometimes pointed out by others); or 3, severe Cushingoid appearance evident to anyone. Approximately two-thirds of patients in EOMG and TAMG have experienced some degrees of Cushingoid appearance, and so did half of the LOMG patients (Fig. 2).

Table 2 Treatment status of myasthenia gravis patients in Japan

	Total n = 640	EOMG n = 280	LOMG n = 214	TAMG n = 145	P-value
PSL administration					
Current dose (mg/day)	4.4 ± 5.9	5.5 ± 6.0	4.4 ± 5.4	6.8 ± 6.8	0.0006†
Total dose during the last 1 year (mg)	1789.2 ± 1946.5	1767.9 ± 1921.7	1436.2 ± 1629.2	2313.7 ± 2270.6	0.045†, 0.003‡
Maximum dose (mg)	27.4 ± 19.3	27.9 ± 19.0	21.9 ± 18.6	34.3 ± 18.6	0.0021*, 0.006†, <0.0001‡
Administration period (years)	5.5 ± 6.1	7.1 ± 0.6	4.2 ± 0.7	8.7 ± 0.8	<0.0001*,‡
Period with a dose of ≥20 mg/day (year)	0.9 ± 2.5	1.2 ± 2.7	0.3 ± 0.8	1.5 ± 3.4	<0.0001*,‡
Period with a dose of ≥10 mg/day (year)	2.7 ± 4.4	3.3 ± 0.3	1.6 ± 2.6	3.3 ± 0.4	<0.0001*,‡
Immunotherapy, %					
CNI	48.8	47.1	47.0	59.6	0.048†
Plasma exchange/plasmapheresis	29.6	28.7	21.7	43.6	0.009†, <0.0001‡
IVIg	9.3	8.9	5.9	14.9	0.015‡
MGFA post-intervention status, %					
CSR	5.6	6.8	6.0	2.8	NS
PR	9.7	8.3	8.8	12.8	NS
MM	35.5	30.9	42.9	33.3	0.018*
I	35.6	37.4	28.6	45.7	0.003‡
U	11.1	12.9	12.9	4.3	0.015†, 0.021‡
W	1.4	1.4	0.9	2.1	NS
E	1.1	2.2	0	0.7	<0.0001*,†
MM or better status with ≤5 mg PSL	43.7	38.1	53.9	39.0	0.0015*, 0.018‡

CNI, calcineurin inhibitors; CSR, complete stable remission; E, exacerbated; I, improved; IVIg, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; NS, not significant; PR, pharmacological remission; PSL, prednisolone; U, unchanged; W, worsened.

*Comparison between early-onset myasthenia gravis (EOMG) and late-onset myasthenia gravis (LOMG).

†Comparison between EOMG and thymoma-associated myasthenia gravis (TAMG).

‡Comparison between LOMG and TAMG.

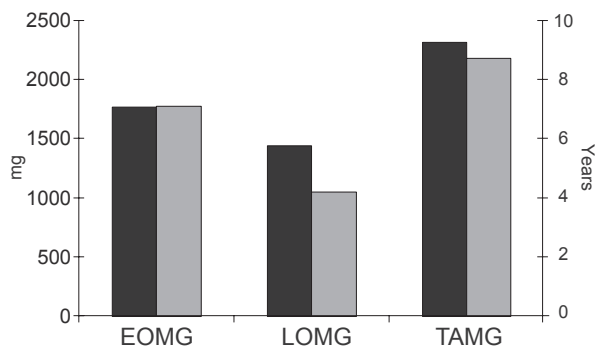

Figure 1 The total dose during the last year and total administration period of prednisolone. Both the total dose during the last year (black bar) and total administration period of prednisolone (gray bar) were highest in thymoma-associated myasthenia gravis (TAMG) patients, followed by early-onset myasthenia gravis (EOMG) patients and lowest in late-onset myasthenia gravis (LOMG) patients.

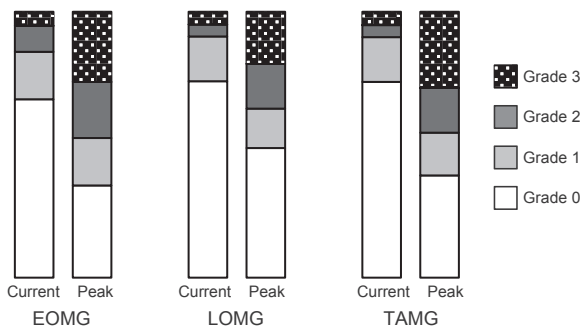

Figure 2 Cushingoid appearance in myasthenia gravis patients. Current status and peak status in the history are shown. Approximately two-thirds of early-onset myasthenia gravis (EOMG) and thymoma-associated myasthenia gravis (TAMG) patients experienced some degree of Cushingoid appearance, as did half of late-onset myasthenia gravis (LOMG) patients.

Comparison between ocular and generalized MG

The demographic and clinical features were compared between pure ocular and generalized MG, and the results are summarized in Table 3. The percentage of females was significantly higher among patients with generalized MG. Age at onset was significantly higher in patients with ocular MG. Severity scale scores and QOL scores were higher in those with generalized MG. There was no difference in positivity for anti-AChR antibodies between the groups. Anti-MuSK antibody was never positive in patients with the ocular form. Referring to the PSL

Table 3 Comparison between ocular and generalized myasthenia gravis

	Ocular MG n = 140	Generalized MG n = 500	P-value
Basic information			
Age at present	61.3 ± 15.7	56.2 ± 16.4	0.0009
Female percentage	56.7%	69.1%	0.006
Disease duration	8.9 ± 10.3	11.2 ± 9.8	<0.0001
Age at onset	52.4 ± 18.5	44.9 ± 17.7	<0.0001
Severity/QOL scales			
QMG score	4.4 ± 3.4	7.8 ± 5.3	<0.0001
MG Composite	2.3 ± 2.9	6.0 ± 6.5	<0.0001
MG-ADL scale	1.9 ± 1.9	3.4 ± 3.4	<0.0001
MG-QOL15-J	9.9 ± 11.3	14.7 ± 12.6	<0.0001
Autoantibodies, %			
Anti-AChR Ab	77.1	79.8	NS
Anti-MuSK Ab*	0.0	12.9	<0.0001
PSL administration			
Current dose (mg/day)	3.7 ± 6.2	5.7 ± 6.0	0.0008
Total dose during the last 1 year (mg)	913.7 ± 1259.1	1957.5 ± 2011.1	<0.0001
Maximum dose (mg)	15.5 ± 15.0	29.4 ± 19.2	<0.0001
Administration period (year)	4.0 ± 6.0	6.9 ± 8.9	<0.0001
Immunotherapy, %			
CNI	22.7	57.6	<0.0001
Plasma exchange/ plasmapheresis	3.5	37.0	<0.0001
IVIg	0.7	11.7	<0.0001
MGFA post-intervention status, %			
CSR	10.6	4.3	0.0039
PR	5.0	10.7	0.0392
MM	48.9	31.8	0.0002
I	17.0	41.7	<0.0001
U	16.4	9.5	0.0098
W	1.4	1.4	NS
E	0.7	1.2	NS
MM or better status with ≤5 mg PSL	61.0	38.8	<0.0001

Ab, antibody, ADL, activities of daily living; CNI, calcineurin inhibitors; CSR, complete stable remission; E, exacerbated; I, improved; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific receptor tyrosine kinase; NS, not significant; PR, pharmacological remission; PSL, prednisolone; QMG, quantitative myasthenia gravis; QOL25-J, Japanese version of the 15-item quality of life scale; U, unchanged; W, worsened.

*Percentage among anti-acetylcholine receptor (AChR) antibody negative patients.

administration, current dose, total dose during the last 1 year, maximum dose and administration period were all significantly higher in the generalized MG group. MGFA post-intervention status showed that MM or better status with ≤5 mg PSL accounted for 61.0% of ocular MG, but just 38.8% of the generalized group achieved this category.

Discussion

Here we report the findings of a nationwide cross-sectional study in Japan, carried out by the JAMG-R. To our knowledge, there is no such detailed study comparing each group in the E-L-T classification. The advantage of the present study is that the JAMG-R consists of highly motivated neurologists who specialize in MG practice, making it possible to enroll consecutive MG patients during a certain period of time. This will make up for the weak points of a previous nationwide epidemiological survey carried out in 2006, where the response rate was considerably low, resulting in some bias of the data.[5] The main limitation of the present study was that pediatric neurologists did not participate in the project; thus, childhood MG is not included in the study.

A total of 640 MG patients were collected and were divided into three groups: EOMG, age at onset ≤49 years, without thymoma; LOMG, age at onset ≥50 years, without thymoma; TAMG, any age at onset, associated with thymoma. There is still no consensus on the definition of EOMG and LOMG with the threshold age at onset ranging from 40 to 65 years, or in the way thymoma-associated cases are assigned. We chose the aforementioned classification for the following reasons. First, we separated thymoma-associated cases, because TAMG has an immunologically distinct background with paraneoplastic components. This group invariably shows positivity for anti-AChR antibody, and is always negative for anti-MuSK antibody (Table 1), which provides more evidence that TAMG has a special background. Second, we divided EOMG and LOMG at an age of 50 years, because histologically, the frequency of hyperplasia peaks between the onset ages of 20 and 40 years, and it becomes rare after 50 years.[17]

Even within the non-thymomatous MG, the present results show the notable difference between EOMG and LOMG. Regarding sex, nearly 80% of patients in the EOMG group were female, whereas the percentages of females and males were almost equal in the LOMG group. This suggests a background difference between EOMG and LOMG. The pure ocular form accounted for just 15.1% of EOMG patients, but its incidence was high (37.8%) among LOMG patients, as previously reported.[23,24] If child-onset MG were studied and included in EOMG, the percentage of ocular myasthenia in EOMG would have been higher, because infantile- and childhood-onset MG contains a higher proportion of ocular MG in Japan.[5]

The frequency of thymoma in our present study was 22.7%. Patients with TAMG show severe symptoms compared with non-thymomatous cases, with high percentages of bulbar symptoms (72.1%) and crisis (23.6%). It is considered that several kinds of striational antibodies (i.e. anti-titin, anti-RyR, anti-Kv1.4), which are frequently detected in TAMG, contribute to the severe condition.[25]

We compared the use of PSL and various other immunotherapies between the groups, and identified that the most extensive immunosuppressive treatments were applied to TAMG patients, followed by EOMG patients, and the minimum amount was received by LOMG patients. The reason TAMG requires aggressive immunotherapy is partly because this group has the most severe clinical symptoms attributed to the presence of striational antibodies. The reason why the least extensive immunotherapy is required in LOMG among the three groups is unclear. One explanation could be ascribed to the high percentage of the ocular form in this group. However, even if we exclude the ocular form, the LOMG group included a higher proportion of the mild generalized form (MGFA II) than did the EOMG and TAMG groups (data not shown). A recent increase in the prevalence of LOMG has been observed worldwide,[11,12,26,27] especially for the elderly-onset group (age at onset ≥65 years) in Japan.[5] There might be some environmental trigger for development of MG in the elderly, which is not as strong as the triggers in thymoma or thymic hyperplasia. In the Caucasian population, LOMG patients also show lower disease activity, favorable prognosis and a high proportion of ocular symptoms,[11,23] but in the previous literature where thymoma-associated cases were not separated, they tended to progress to severe disease status.[9]

"MM or better status with ≤5 mg PSL", which includes CSR, PR and MM with the cut-off of PSL dose at 5 mg/day, correlates well with MG-QOL15-J, and is recommended as a treatment target for MG.[22] This status was achieved in half of LOMG patients, but only in one-third of EAMG and TAMG patients. Furthermore, many patients suffered from Cushingoid appearance as a result of PSL treatments. Thus, the treatment status in MG patients is still far from sufficient, especially in EOMG and TAMG patients. A refined therapeutic strategy and development of new drugs for MG are mandatory.[28]

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