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Late-onset myasthenia gravis is predisposed to become generalized in the elderly

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ABSTRACT

Objective: The continuous increase in the number of patients presenting with late-onset myasthenia gravis (LOMG) underscores the need for a better understanding of the clinical course and the establishment of an optimal therapeutic strategy. We aimed to clarify factors associated with clinical outcomes in LOMG.
Methods: We retrospectively reviewed the clinical profiles of 40 patients with early-onset MG (EOMG) (onset age: 49 years or younger), 30 patients with non-elderly LOMG (onset age: 50–64 years), and 28 patients with elderly LOMG (onset age: 65 years or older) and compared the subgroups according to onset age and thymus status. The evaluated parameters were MGFA classification before treatment, MG-ADL score, complicating diseases, antibody titer, treatment, and MGFA post-intervention status.
Results: Elderly LOMG patients showed transition to generalized symptoms at a higher frequency and underwent thymectomy less frequently than EOMG and non-elderly LOMG patients ($p < 0.001$). The frequencies of crisis and plasmapheresis were significantly lower in thymectomized LOMG patients without thymoma than in thymectomized LOMG patients with thymoma or non-thymectomized LOMG patients ($p < 0.01$, $P < 0.05$, respectively). However, the outcome was not significantly different. All of the thymectomized LOMG patients without thymoma presenting with hyperplasia or thymic cyst had a favorable clinical course.
Conclusions: Our study showed that elderly LOMG patients are more prone to severity, suggesting that they require aggressive immunomodulatory therapy.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction that causes fluctuating skeletal muscle weakness [1]. Most cases present with antibodies to the skeletal muscle nicotinic acetylcholine receptor (AChR); in cases without anti-AChR antibody, autoantibodies to muscle-specific tyrosine kinase receptor (MuSK) or low-density lipoprotein 4 (Lrp4) are targets of the autoimmune attack [2]. The prevalence is estimated at 15–179 patients per one million people, and several researchers have reported an increasing incidence of late-onset MG (LOMG) worldwide [3–7]. Life-threatening respiratory weakness, called myasthenic crisis, occurs in approximately 15% of patients [3]. Treatment of MG includes short-term symptomatic treatment, chronic immunosuppression, and surgical intervention. For severe disease or crisis, immunomodulatory therapies, such as plasmapheresis (PE) or intravenous immunoglobulin (IVIg), are prescribed [3]. Oral corticosteroids remain the first-line treatment and are still the most commonly used for long-term immunosuppression [8]. Whereas corticosteroids are highly effective against MG, they usually must be given chronically in combination with a steroid-sparing immunosuppressive drug (e.g., azathioprine or tacrolimus) to reduce significant risks of adverse events [8,9]. Elderly patients are vulnerable to complications from high-dosage or long-term oral corticosteroid therapy [10]. Whereas thymectomy is considered the standard therapy for thymomatous MG or generalized MG without thymoma, the benefits of thymectomy in LOMG without thymoma are assumed to be minimal. This assumption is based on the fact that thymus tissue becomes

Abbreviations: EOMG, early-onset myasthenia gravis; LOMG, late-onset myasthenia gravis; AChR, acetylcholine receptor; MGFA, Myasthenia Gravis Foundation of America; MG-ADL, myasthenia gravis activities of daily living score; PIS, MGFA post-intervention status; DM, diabetes mellitus; ChE-I, cholinesterase inhibitor; PSL, prednisolone; IVIg, intravenous immunoglobulin; PE, plasmapheresis.

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atrophic and is replaced with fat with age [8,10]. Some researchers, however, believe that thymectomy may benefit generalized LOMG patients, particularly LOMG patients with thymic hyperplasia [11]. To understand and address these issues, we investigated how clinical features in LOMG were influenced by onset age and thymus status.

2. Methods

We retrospectively conducted a review of the clinical records of 40 early-onset MG (EOMG) and 58 LOMG patients who were treated and followed up at our institution. Data of all patients with disease onset between the years 1978 through 2014 and treated at Tokushima University Hospital were analyzed. The eligibility criteria were onset age of 49 years or younger for EOMG and onset age of 50 years or older for LOMG, as well as fulfillment of diagnostic criteria for MG [7]. We tabulated age, gender, onset age, body weight, disease duration, disease severity, anti-AChR antibody titer, occurrence of crisis, coexisting illness (e.g., extrathymic malignancy, autoimmune disease, diabetes mellitus [DM]), thymic histology, and treatment. Disease severity and distribution were graded according to the classification of the Myasthenia Gravis Foundation of America (MGFA) and scored on the basis of the myasthenia gravis activities of daily living score (MG-ADL). In addition, we surveyed patients presenting with ocular symptoms at the onset and who developed generalized symptoms at later time, and defined ocular type as those who did not show generalized symptoms in the entire clinical course. We checked whether DM existed before or after the initiation of PSL; in the latter case, it was classified as secondary DM. Histological analyses of the thymus were performed in patients who underwent thymectomy.

We determined the therapies received by individual patients, including cholinesterase inhibitors (ChE-Is), PSL, immunosuppressive drugs, PE, IVIg, and thymectomy. We checked MG-ADL scores before and after treatment (at 1 and 3 years). Oral PSL dosage was low initially and gradually increased to the maintenance dosage for patients who were not sufficiently controlled by ChE-I. The maximum PSL dosage before tapering and the PSL dosage at 1 and 3 years from the initiation of PSL were examined. The maximum PSL dosage was divided into three categories: low dose (less than 10 mg/day), middle dose (more than 10 mg/day and less than 0.75 mg/day/kg), and high dose (0.75–1.0 mg/kg/day). We also assessed the outcome on the basis of MG-ADL scores, PSL dosage, and MGFA post-intervention status (PIS) at 3 years after the treatment.

First, we classified the patients according to onset age into EOMG (onset age ≤ 49), non-elderly LOMG (onset age 50–64), and elderly LOMG (onset age ≥ 65). Second, we classified the LOMG patients according to thymus status into three groups: thymectomized LOMG with thymoma, thymectomized LOMG without thymoma, and non-thymectomized LOMG. The clinical profiles of these groups were analyzed. This study was approved by the Ethics Committee of Tokushima University Hospital. All subjects gave written informed consent for their participation.

Commercially available statistics software was used for data analysis (SPSS20). Differences between two groups or among three groups were compared. The Student *t* test, the Kruskal–Wallis test, the chi-square test, and the Mann–Whitney *U* test were employed. Differences were considered statistically significant at $p < 0.05$.

3. Results

We enrolled 40 EOMG patients (female, 35; age, 33.4 ± 9.8 [mean ± SD] years), 30 non-elderly LOMG patients (female, 15; age, 56.1 ± 4.4 years), and 28 elderly LOMG patients (female, 17; age, 74.4 ± 4.8 years). EOMG was significantly female-predominant. The ocular type (MGFA I) was significantly higher in non-elderly LOMG patients than in the other two groups ($p < 0.01$), whereas the generalized type was significantly higher in EOMG and elderly LOMG patients than in non-elderly LOMG patients ($p < 0.001$). However, elderly LOMG patients presenting with ocular symptoms at the onset subsequently developed generalized symptoms at a much higher frequency than the corresponding EOMG or non-elderly LOMG patients ($p < 0.001$). There was no significant difference in the MG-ADL score among the three groups (Fig. 1A). 22.5% of EOMG patients, 16.7% of non-elderly LOMG patients, and 3.6% of elderly LOMG patients presented with other autoimmune diseases, such as thyroid disease and rheumatoid arthritis. LOMG patients had significant extrathymic malignancy compared with EOMG patients ($p < 0.05$). Hyperplasia was confirmed in 25% of EOMG patients and 10% of non-elderly LOMG patients, whereas no hyperplasia was noted in elderly LOMG patients. All of the three patients presenting with hyperplasia in the non-elderly LOMG group were female and their onset age was 54.7 ± 4.2 years. The frequency of DM

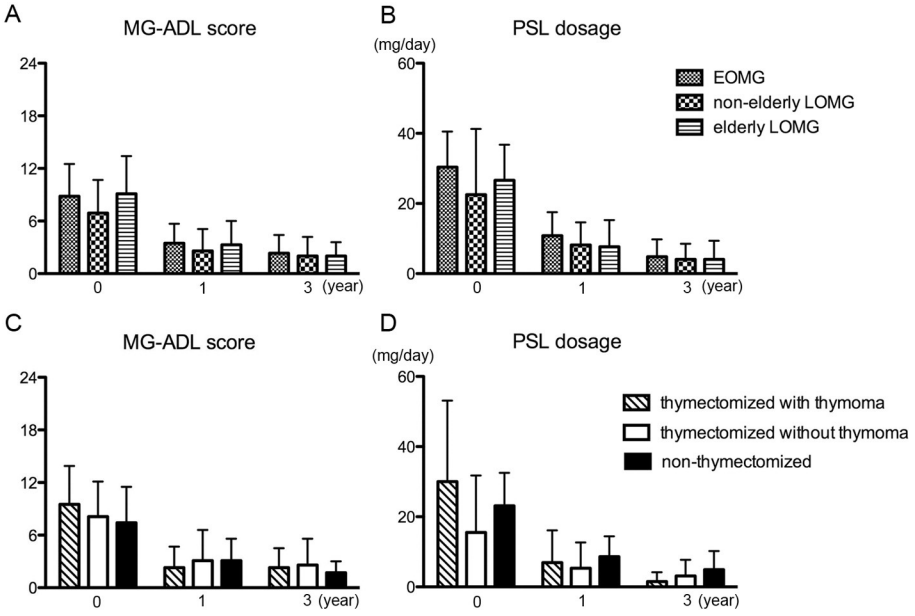

Fig. 1. Clinical outcome and steroid dosage up to 3 years after treatment. MG-ADL score before (0 year) and 1 and 3 years after treatment (A, C). Oral PSL (mg/day) represents the maximum dosage (0 year) and the dosage at 1 and 3 years after initiation of PSL (B, D). *$p < 0.05$.

was significantly increased in the two LOMG groups ($p < 0.001$). More non-elderly LOMG patients underwent thymectomy than elderly LOMG patients ($p < 0.001$). There was no significant difference in the maximum PSL dosage among the three groups, but the number of patient receiving a low-dose PSL was significantly higher in the non-elderly LOMG than that in the other two groups ($p < 0.05$). Calcineurin inhibitors were administrated for more than 50% of LOMG, especially elderly LOMG patients. IVIg was administered much more often in elderly LOMG patients. None of the LOMG patients showed complete stable remission (CSR), but they achieved minimal manifestation (MM) with a PSL dosage of 10 mg/day or less (Table 1, Fig. 1A–B).

We compared the clinical profiles of 22 patients with thymectomized LOMG (female, 14; onset age, 58.9 ± 7.8 years) and 36 patients with non-thymectomized LOMG (female, 18; onset age, 68.6 ± 9.8 years). The thymectomized LOMG patients were further classified into two groups: 10 patients without thymoma and 12 patients with thymoma. The thymectomized group was significantly younger than the non-thymectomized group ($p < 0.01$). Crisis occurred most often in thymectomized LOMG patients with thymoma ($p < 0.01$), who were treated with PE most frequently ($p < 0.05$). The maximum PSL dosage in the thymectomized LOMG without thymoma group was lower than that in the thymectomized LOMG with thymoma group or the non-thymectomized LOMG group, although the difference was not significant. AChR titer in the thymectomized LOMG without thymoma group was the highest. Notably, 3 of 10 thymectomized LOMG patients without thymoma presented with thymic hyperplasia, 1 had a giant thymic cyst, 4 had involuted thymuses, and 2 had an unknown histology. In addition, all of the thymectomized LOMG patients with hyperplasia or thymic cyst had a favorable clinical course with no worsening of MG symptoms (data not shown). There was no significant difference in post-treatment MG-ADL score, PIS, and post-treatment steroid dosage among the three groups (Table 2, Fig. 1C–D).

4. Discussion

This is a study that aimed to comprehensively demonstrate the influence of several factors, such as onset age and thymus status, on the clinical outcome of LOMG patients. We found that elderly LOMG patients showed transition to the generalized type at a high frequency, and some non-elderly LOMG patients had benefitted from the thymectomy, even though thymoma did not exist.

The incidence of ocular MG in our non-elderly LOMG group was similar to that in a previous report [7], whereas the incidence was low in the elderly LOMG group, indicating that more elderly LOMG patients with the ocular type transitioned to the generalized type in the clinical course. A low PSL dose was frequently administered to non-elderly LOMG patients, which was a possible indication of the less generalized type. Clinicians preferred middle-dose PSL rather than high-dose PSL for elderly LOMG patients because of the coexistence of such illnesses as DM or to avoid adverse effects. Since advantages of early use of calcineurin inhibitors have been reported, calcineurin inhibitors were administrated for 78.6% of elderly LOMG patients [12]. A recent study conducted in Japan demonstrated that a higher PSL dose did not ensure better outcome in MG [13]. In this study, we also evaluated clinical features according to the maximum PSL dosage, but found no significant difference in PIS among low dose, middle dose, and high dose (data not shown). Furthermore, no CSR was detected and the LOMG patients had MM, suggesting that the disease could be finally controlled by

Table 1
Clinical profiles of EOMG, non-elderly LOMG, and elderly LOMG patients.

	EOMG (n = 40)	Non-elderly LOMG (n = 30)	Elderly LOMG (n = 28)
Onset age (year)	33.4 ± 9.8 (11–49)	56.1 ± 4.4 (50–64)	74.4 ± 4.8 (66–82)
Sex (male/female)	5/35 [d, f]	15/15 [d,e]	11/17 [e, f]
Disease duration (month)	13.4 ± 16.4 (0.5–84.0) [j]	4.8 ± 4.8 (0.1–22.0) [j]	7.4 ± 9.4 (0.2–36.0)
Body weight (kg)	53.5 ± 14.6 (30.0–90.0)	60.2 ± 12.7 (33.7–88.3)	52.4 ± 11.5* (33.0–75.0)
Ocular type (n, (%))	4 (10.0) [d]	12 (40.0) [d, e]	2 (7.1) [e]
Generalized type (n, (%))	36 (90.0) [g]	18 (60.0) [g, h]	26 (92.3) [h]
Transition to generalized type (n, (%))	9 (22.5) [g, i]	10 (33.3) [g, h]	16 (57.1) [h, i]
Crisis (n, (%))	9 (22.5)	3 (10.0)	7 (25)
MGFA classification before treatment	I 4, II 16, III 16, IV 1, V 3	I 12, II 7, III 8, IV 0, V 3	I 2, II 9, III 9, IV 1, V 7
AChR positivity (n, (%))	36 (90.0)	28 (93.3)	23 (82.1)
Anti-AChR Ab titer (nmol/L) (mean ± SD)	287.9 ± 583.4 (0.3–2700.0)	232.5 ± 1033.0 (1.1–5500.0)	26.7 ± 21.7 (0.6–80.5)
Autoimmune disease (n, (%))	9 (22.5)	5 (16.7)	1 (3.6)
Extrathymic malignancy (n, (%))	0 (0.0) [a, c]	5 (16.7) [a, b]	2 (7.1) [b, c]
Thymus status (n, (%))			
Thymoma	10 (25.0)	8 (26.7)	4 (14.3)
Hyperplasia	10 (25.0) [d, f]	3 (10) [d, e]	0 (0) [e, f]
DM (n, (%))	2 (5.0) [g, i]	8 (26.7) [g, h]	10 (35.7) [h, i]
Secondary DM (n, (%))	1 (2.5)	3 (10)	3 (10.7)
Treatment (n, (%))			
Thymectomy	32 (80.0) [g, i]	17 (56.7) [g, h]	5 (17.9) [h, i]
ChE-I	39 (97.5)	30 (100.0)	27 (96.4)
Steroid	25 (62.5)	20 (66.7)	23 (82.1)
Low dose	3 [a]	9 [a, b]	1 [b]
Middle dose	13	7	15
High dose	9	4	7
Calcineurin inhibitors	22 (55.0)	17 (56.7)	22 (78.6)
PE	10 (25.0)	5 (16.7)	9 (32.1)
IVIg	4 (10.0) [c]	1 (3.3) [b]	8 (28.5) [b, c]
PIS (in 3 years)	CSR 5 [a, c], I 3, MM1 4, MM2 13, MM3 15	MM1 3, MM2 5, MM3 18	MM0 1, MM1 2, MM2 10, MM3 6

Each value indicates mean ± SD (range).
Significantly different between EOMG and non-elderly LOMG, a = $p < 0.05$, d = $p < 0.01$, and g = $p < 0.001$ in the chi-square test or Fisher's exact test.
Significantly different between non-elderly LOMG and elderly EOMG, b = $p < 0.05$, e = $p < 0.01$, and h = $p < 0.001$ in the chi-square test or Fisher's exact test.
Significantly different between EOMG and elderly LOMG, c = $p < 0.05$, f = $p < 0.01$, and i = $p < 0.001$ in the chi-square test or Fisher's exact test.
Significantly different between EOMG and non-elderly LOMG, $p < 0.05$ in the Kruskal–Wallis test.
ChE-I = cholinesterase inhibitor, PE = plasmapheresis, IVIg = intravenous immunoglobulin, PIS = MGFA post-intervention status MM = minimal manifestation, NA = not available, NS = not significant.

Table 2
Clinical profiles of thymectomized and non-thymectomized LOMG patients.

	Thymectomized LOMG with thymoma (n = 12)	Thymectomized LOMG without thymoma (n = 10)	Non-thymectomized LOMG (n = 36)
Age at thymectomy (year, mean ± SD)	60.3 ± 8.8 (50–76)	57.2 ± 7.0 (50–74)	NA
Sex (male/female)	4/8	4/6	18/18
Disease duration (month, mean ± SD))	4.1 ± 4.4 (0.1–12.0)	7.8 ± 6.2 (0.5–22.0)	6.2 ± 8.5 (0.2–36.0)
Ocular type (n, (%))	8 (66.7)	6 (60.0)	25 (69.4)
Crisis (n, (%))	6 (50.0)[a]	0 (0)[a]	4 (11.1)[a]
Thymic histology	NA	Hyperplasia 3, thymic cyst 1, and involuted thymus 4	NA
AChR positivity (n, (%))	12 (100)	9 (90.0)	30 (88.2)
Anti-AChR Ab titer (nmol/l, mean ± SD)	28.4 ± 13.5 (15.0–58.0)	680.6 ± 1807.7[b] (14.0–5500)	22.0 ± 21.8[b] (0.6–91.0)
Treatment (n, (%))			
ChE-I	12 (100)	10 (100)	35 (97.2)
Steroid	11 (91.7)	7 (70.0)	25 (69.4)
Calcineurin inhibitors	8 (66.7)	7 (70.0)	24 (66.7)
PE	7 (58.3)[c]	0 (0)[c]	7 (19.4)[c]
IVIg	1 (8.3)	0 (0)	8 (22.2)
PIS (in 3 years)	MM1 1, MM2 2, and MM3 7	MM1 1, MM2 2, and MM3 5	MM0 1, MM1 3, MM2 11, and MM3 12

Each value indicates mean ± SD (range).
[c] Significantly different between thymectomized LOMG without thymoma and thymectomized LOMG with thymoma or non-thymectomized LOMG, $p < 0.05$ in the chi-square test.
[a] Significantly different between thymectomized LOMG without thymoma and thymectomized LOMG with thymoma or non-thymectomized LOMG, $p < 0.01$ in the chi-square test.
[b] Significantly different between thymectomized LOMG without thymoma and non-thymectomized LOMG, $p < 0.001$ in the Kruskal-Wallis test ChE-I: cholinesterase inhibitor; PE: plasmapheresis; IVIg: intravenous immunoglobulin; PIS: MGFA post-intervention status MM = minimal manifestation, NA = not available, NS = not significant.

immunomodulatory drugs and/or ChE-I. Our results were consistent with the previous observation that overall prognosis was favorable but CSR was rare in LOMG [14].

There is an ongoing debate on the application of thymectomy to non-thymomatous MG patients, particularly LOMG patients [3]. Several studies reported that it was unlikely that attempts to remove the thymus of older patients would be rewarding [10,15]. On the other hand, Kawaguchi et al. indicated that thymectomy is a potentially effective treatment for LOMG without thymoma but with mild generalized symptoms [16]. Indeed, our results demonstrated no significant difference in MG-ADL score and PIS among thymectomized LOMG with thymoma, thymectomized LOMG without thymoma, and non-thymectomized LOMG groups. This was in line with a previous study showing that outcome measures did not significantly differ between thymectomized and non-thymectomized LOMG groups [16]. Importantly, we confirmed that the proportion of crisis in thymectomized LOMG patients without thymoma was significantly lower than that in thymectomized LOMG patients with thymoma or non-thymectomized LOMG patients. A postmortem study showed that no germinal centers were detected in the thymuses of MG patients over 60 years old [17]. In the present study, the cases of LOMG with hyperplasia were female and onset age was below 60 years old. Taken together, thymectomy may be a reasonable treatment option for LOMG cases with onset age younger than 60 years old.

In conclusion, the present study shows that elderly LOMG patients are predisposed to become generalized than non-elderly LOMG patients. Our study also provides a perspective on aggressive immunomodulatory therapies for elderly LOMG.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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