eNeurologicalSci 2 (2016) 17–20

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: http://ees.elsevier.com/ensci/

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

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ARTICLE INFO

Article history:
Received 28 November 2015
Received in revised form 8 February 2016
Accepted 10 February 2016
Available online 11 February 2016

Keywords:
Late-onset myasthenia gravis
Elderly
Crisis
Thymectomy
Hyperplasia
Steroid

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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http://dx.doi.org/10.1016/j.ensci.2016.02.004

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

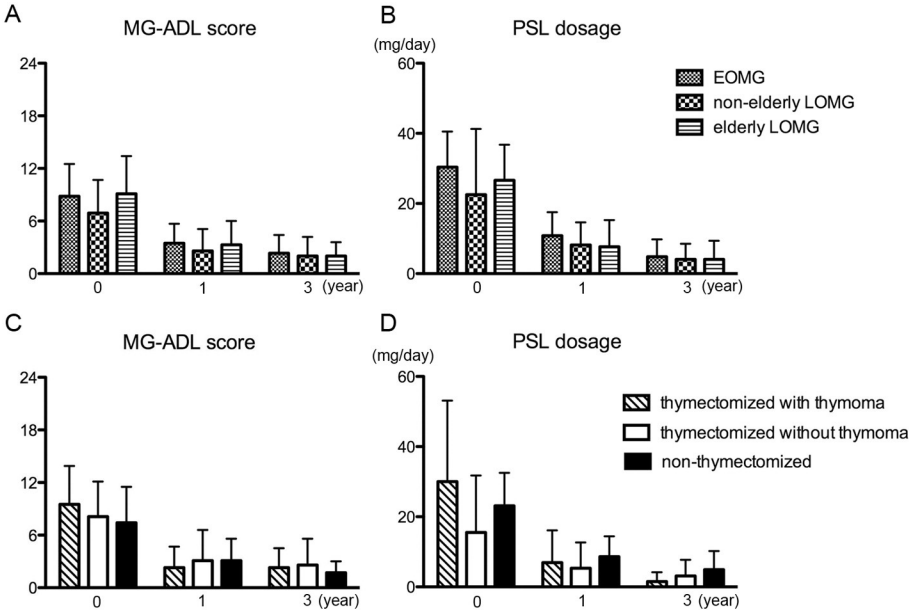

Fig. 1. Clinical outcome and steroid dosage up to 3 years after treatment. MG-ADL score before (0 year) and 1 and 3 years after treatment (A, C). Oral PSL (mg/day) represents the maximum dosage (0 year) and the dosage at 1 and 3 years after initiation of PSL (B, D). *$p < 0.05$.