Spotlight on MuSK Positive Myasthenia Gravis: Clinical Characteristics, Treatment and Outcomes

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Research Article

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Abstract

Background: To investigate the clinical characteristics, treatment and outcomes of myasthenia gravis with antibodies to the muscle-specific tyrosine kinase (MuSK-MG).

Methods: We retrospectively reviewed 21 patients with confirmed MuSK-MG between January 2012 to January 2020 in our center. Detailed clinical data and long-term follow up information were summarized.

Results: Females (17/21, 81%) predominated in MuSK-MG and the mean age of onset in this group was 51.86±16.16 years. MuSK-MG patients was divided into three subgroups according to the symptom of muscle weakness at onset: ocular myasthenia gravis (OMG, 47.6%), bulbar myasthenia gravis (BMG, 42.9%), and generalized myasthenia gravis (GMG, 9.5%). The mean progression time from symptoms onset to other muscle groups involvement in OMG patients was 4.38±2.54 months. Pyridostigmine bromide was adopted in 81.0% patients and 90.5% patients received corticosteroids. Compared to the usage in hospital, the median daily dose of corticosteroids decreased significantly at the last follow-up. 85.7% patients received a long-term follow-up with an average time of 1202.17 ± 976.73 days. At the end of the follow-up period: 4.8% patient received complete stable remission, 42.9% patients were in minimal manifestations, 19.0% had improved, 4.8% experienced an unchanged condition and 9.5% patients died.

Conclusion: Female patients were more prevalent in this study and MuSK-MG patients had a rapid progress to a generalized state. Although about 50% MuSK-MG patients can achieve a favorable outcome with conventional immunosuppressants, complete stable remission is rare and about 15% respond poorly, more effective medications should be explored in these patients.

Background

Myasthenia gravis (MG) is an autoimmune disease that affects the neuromuscular junction, usually leads to skeletal muscle weakness and fatigability[1, 2]. Patients with MG who have no detectable circulating antibodies (Abs) to acetylcholine receptor (AChR) are frequently defined as having seronegative MG (SNMG)[2]. In 2001, a novel serum antibody against muscle-specific tyrosine kinase (MuSK) was revealed in SNMG patients, which was found in 70% of AChR-Ab-seronegative MG patients[3]. As a subgroup of MG, MuSK-Ab-positive patients often suffer more severe bulbar muscle weakness and present various clinical characteristics. Despite previous reports showed the symptom of MuSK-MG patients may associated with region and race[4, 5], studies about the relevant clinical features and treatment outcomes in Asian are rare[6]. Hence, the specific disease course, especially in the response to standard treatment and prognosis of MuSK-MG patients still need further observation and investigation. We retrospectively analyzed the clinical characteristics, treatment and prognosis of MuSK-MG patients in our medical center in China, aiming to improve the clinicians’ further understanding of the disease.

Methods

Study Design and Data Collection

This was a retrospective single-center study. This study was approved (2020-KY-231) by the ethics committee of the First Affiliated Hospital of Zhengzhou University, and the written informed consent for the use of clinical data was waived by the ethics committee. The clinical data of patients who were diagnosed of MG at the First Affiliated Hospital of Zhengzhou University from January 2012 to January 2020 were retrospectively reviewed and documented in a well-constructed MG database. The baseline characteristics were collected from the hospital information system. Autoantibody tests were double checked with the data from the Department of Neuroimmunology in the Henan Institute of Medical and Pharmaceutical Sciences. The inclusion criteria were a confirmed diagnosis of MG and seropositive for anti-MuSK Ab. Patients were regularly followed up at the out-patient department and those who stopped visiting us were called for the last follow up in January 2021. The clinical, diagnostic, therapeutic, and prognosis data of these patients, including gender, age of onset, initial symptoms, disease progression, clinical classification, Myasthenia Gravis Foundation of America (MGFA) clinical class, disease severity, pharmacological, electrophysiological, and serological findings, results of thymus examination, comorbidities, therapeutic options, and prognosis, were analyzed.

Patients and Diagnosis Criteria

This study comprised 21 patients with confirmed MuSK-MG, 4 males and 17 females. All patients were diagnosed MG by typical myasthenic symptoms with diurnal variation, and at least one of the following results: positive pharmacologic response to oral pyridostigmine or corticosteroids; positive electrophysiological tests; positive repetitive nerve stimulation (RNS) test; seropositive for AChR Ab or MuSK Ab or low-density lipoprotein receptor-related protein (LRP4) Ab. For each participant, the MGFA classification was used to evaluate the clinical status and disease severity at the onset of myasthenic symptoms and at each follow-up. The MGFA Postintervention Status was used to assess the clinical state after treatment: Complete Stable Remission (CSR), Pharmacologic Remission (PR), Minimal Manifestation (MM), and change in status[7].

Detection of AChR-Ab and MuSK-Ab

AChR-Ab levels were tested using a standard AChR-Ab ELISA Kit (RSR, UK) following the manufacturer's instructions, with a cut-off value of 0.45 nM. All the sera were measured by a radioimmunoassay (RIA) for MuSK antibody detection. Using the MuSK-Ab RIA Kit (RSR, UK) followed the manufacturer's instructions. A cut-off value of 0.05 nM was used to score MuSK positive samples[8].

Statistical Analysis

IBM SPSS statistics 21 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were presented as means (SD), and categorical variables were summarized as numbers and frequencies. Normally distributed continuous variables analysis was used by Student t test. Mann whitey test
was used for non-normally distributed data analysis and Chi-square test was used for categorical variables. P value smaller than 0.05 was considered statistically significant.

Results

Detailed clinical data of the 21 MuSK-MG patients are listed in Table 1

| Characteristic                          | Males (n = 4) | Females (n = 17) | Total (n = 21) |
|----------------------------------------|--------------|-----------------|---------------|
| Mean age in years (SD)                 | 66.25 ± 8.62 | 49.24 ± 16.68   | 52.48 ± 16.75 |
| Mean age at onset in years (SD)        | 66.00 ± 8.41 | 48.53 ± 15.86   | 51.86 ± 16.16 |
| First symptom                          |              |                 |               |
| Ocular                                 | 2/4          | 8/17            | 10/21         |
| Bulbar                                 | 1/4          | 7/17            | 8/21          |
| Neck                                   | 0/21         | 1/21            | 1/21          |
| Limb                                    | 1/4          | 1/17            | 2/21          |
| Clinical subtypes at onset             |              |                 |               |
| Ocular                                 | 2/4          | 8/17            | 10/21         |
| Generalized                            | 2/4          | 9/17            | 11/21         |
| MGFA status at onset                   |              |                 |               |
| I                                       | 2/4          | 8/17            | 10/21         |
| II                                      | 1/4          | 8/17            | 9/21          |
| III                                     | 1/4          | 1/17            | 2/21          |
| IV                                      | 0/4          | 0/17            | 0/21          |
| V                                       | 0/4          | 0/17            | 0/21          |
| AChR positive                          | 0/4          | 1/17            | 1/21          |
| RNS abnormalities                      | 2/4          | 14/17           | 16/21         |
| Thymoma present                        | 0/4          | 0/17            | 0/21          |
| Myasthenic crises                      | 1/4          | 5/17            | 6/21          |
| Neostigmine test                       | 3/4          | 15/17           | 18/21         |
| Medications at early follow up         |              |                 |               |
| Pyridostigmine bromide                 | 1/4          | 5/17            | 6/21          |
| Corticosteroids                        | 2/4          | 9/17            | 11/21         |
| Tacrolimus                              | 2/4          | 0/17            | 2/21          |

A total of 21 MuSK-MG patients were included in this study. Females predominated in this group (17/21, 81%) and only 4 (4/21, 19%) were men. The mean age at onset was 51.86 ± 16.16 (66.00 ± 8.41 years for male patients, and 48.53 ± 15.86 years for female ones). The median follow-up time in the whole group was 1134.05 ± 928.86 (range 230–3440) days and 3 patients refused to provide any information at the last time. The overall follow periods of the 3 patients who lost to the last follow up were 0 days, 40 days and 230 days respectively.

The initial symptom of musk mg

At onset, 10 patients had ocular muscle weakness (ptosis, 6/21 (28.6%); double vision, 5/21 (23.8%)), 8 had bulbar weakness (dysphagia, 4/21 (19.0%); dysarthria, 4/21 (19.0%); respiratory muscle weakness, 1/21 (4.8%)), 1 had neck muscle weakness and 2 had limb weakness. According to the symptom of muscle weakness at onset, MuSK-MG patients was divided into ocular myasthenia gravis (OMG, predominant manifestation are ptosis and diplopia) in 10 cases (47.6%), bulbar myasthenia gravis (BMG, predominant manifestation are impaired speech, difficulty swallowing or chewing and shortness of breath) in 9 cases (42.9%), and generalized myasthenia gravis (GMG, predominant manifestation is limb weakness) in 2 cases (9.5%).
Testing

Neostigmine testing was performed in 90.5% of patients and was positive in 57.9% of those tested, occasionally with cramps and fasciculations. Electrodiagnostic testing measured by Repetitive Nerve Stimulation (RNS). RNS was performed in 76.2% patients with a positive rate of 37.5%. The abnormal performance of RNS was frequently showed in facial and proximal upper extremity muscles. All 21 patients received mediastinum CT scan as a routine examination. The AChR-Ab and MuSK-Ab expression were co-exist in patient 1 (a 50-year-old female, presented ptosis at onset and was in minimal manifestations at the last follow-up after a series of treatment). No thymomas were detected and the anti-Titin Ab test showed a consistent result (negative in 100%).

Serial studies of clinical status

We recorded the detailed treatment and physical condition throughout the course of the disease in Table 2. Disease severity grade was measured according to the MGFA classification during the disease’s course (at onset, in the maximally deteriorated state, after or during treatment). Table 2 provides serial drug dosage and MGFA scores during a long-term follow-up. At onset, MGFA classification of MuSK-Ab positive patients was evaluated, OMG in 10 cases(all patients were grade I), BMG in 9 cases(7 patients were in grade IIb, 2 patients were in grade IIIb), GMG in 2 cases(2 patients were in grade IIa). We recorded the time from the first symptom to the involvement of other muscle groups and the time from onset to myasthenic crisis. The ten OMG patients all (100%) had generalized weakness progression and the mean progression time from the onset of symptoms to other muscle groups involvement was 4.38 ± 2.54 months. Six patients (4/6 of OMG patients, 2/6 of BMG patients) suffered from MG crisis during hospitalization and the median time from the onset to myasthenic crisis was 7.76 ± 4.48 months. As disease progressed, the severity grades of OMG patients(grade I at onset) were raised in a short period, 7/10(70%) patients had extraocular muscles involved(MGFA grade IIb), 3/10(30%) patients experienced difficulty in swallowing or respiration(MGFA grade IIIb).
| (1) OMG patients | (2) BMG patients |
|------------------|------------------|
| **N** | **Gender** | **Age at onset (years)** | **Duration (days)** | **MGFA classification** | **Treatment** | **N** | **Gender** | **Age at onset (years)** | **Duration (days)** | **MGFA classification** | **Treatment** |
| 1 | female | 48 | 0 | N | N | N | 11 | female | 50 | 0 | N | N |
| 30 | | | | N | N | N | 270 | | | | N | N |
| 82 | | | | NA | Y | Y | N | 420 | | | | N | N |
| 87 | | | | N | Y(240mg) | Y(45mg) | N | 12 | female | 66 | 0 | N | N |
| 360 | | | | N | Y(120mg) | Y(10mg) | N | 25 | | | | N | N |
| 2 | male | 71 | 0 | N | N | N | 40 | | | | N | N |
| 150 | | | | N | N | N | 20 | | | | N | N |
| 260 | | | | N | Y(360mg) | Y(60mg) | N | 50 | | | | N | N |
| 380 | | | | N | Y(360mg) | Y(60mg) | N | | | | N | N |
| 3 | female | 50 | 0 | N | N | N | 1255 | | | | N | N |
| 76 | | | | N | N | N | 371 | | | | N | N |
| 95 | | | | N | Y(80mg) | N | 371 | | | | N | N |
| 300 | | | | N | Y(80mg) | N | 380 | | | | N | N |
| 1020 | | | | N | Y(90mg) | N | 1320 | | | | N | N |
| 4 | female | 37 | 0 | N | N | N | 15 | | | | N | N |
| 25 | | | | N | Y(180mg) | N | 192 | | | | N | N |
| 74 | | | | N | Y(270mg) | Y(60mg) | N | 198 | | | | N | N |
| 180 | | | | N | Y(360mg) | Y(40mg) | N | 543 | | | | N | N |
| 210 | | | | N | Y(180mg) | Y(30mg) | N | 1065 | | | | N | N |
| 306 | | | | N | Y(90mg) | Y(25mg) | N | 1065 | | | | N | N |
| 5 | female | 31 | 0 | N | N | N | 1490 | | | | N | N |
| 180 | | | | N | N | N | 1230 | | | | N | N |
| 385 | | | | N | N | N | 1190 | | | | N | N |
| 393 | | | | N | N | N | 1255 | | | | N | N |
| 565 | | | | N | Y(180mg) | Y(60mg) | N | 223 | | | | N | N |
| 1105 | | | | N | Y(180mg) | N | 230 | | | | N | N |
| 2903 | | | | N | Y(90mg) | N | 1130 | | | | N | N |
| 6 | female | 40 | 0 | N | N | N | 15 | | | | N | N |
| 120 | | | | N | N | N | 36 | | | | N | N |
| 502 | | | | N | N | N | 840 | | | | N | N |
| 521 | | | | N | N | N | 910 | | | | N | N |
| 1855 | | | | N | N | N | 1170 | | | | N | N |
| 7 | female | 49 | 0 | N | N | N | 366 | | | | N | N |
| 30 | | | | N | N | N | 1230 | | | | N | N |
| 270 | | | | N | N | N | 1255 | | | | N | N |

PYR, pyridostigmine bromide; CS, corticosteroids; Tacro, tacrolimus; NA, not available; GE, symptoms processed to generalized myasthenia gravis; MC, MG cr

* Chinese herbal medicine; # IVIg (intravenous immunoglobulin); #AZA (azathioprine, 100mg); #plasm exchange 5 times; ^patients lost at the last follow up
Treatment

The detailed treatment at each point of patients during the disease course was showed in Table 2. We adopted the MGFA post-intervention status as the method to evaluate the therapy effect. According to the guideline, AChE-I (acetylcholinesterase inhibitor) treatment using pyridostigmine bromide was adopted in 17 patients (81.0%) as a symptomatic medication. In terms of change in relevant medications, we recorded the exact dose during the follow-up. The starting dose of pyridostigmine bromide in this study was unavailable, while the average early follow-up dose was 225 mg (15 patients received $\geq 180$ mg during the severe condition). Compared to BMG patients, the median daily dose of pyridostigmine bromide ($258.8 \pm 138.8$ vs $191.3 \pm 75.1$ mg, $P = 0.09$) did not change statistically in OMG patients. Nineteen patients (90.5%) received corticosteroids and the median peak dose of OMG patients was $55.8 \pm 10.7$, compared with BMG patients ($42.5 \pm 17.5$, $P = 0.16$). Compared to the usage in hospital, the median daily dose of corticosteroids decreased significantly (Fig. 1B, $46.8[20–60]$ vs $22.7[10–50]$ mg, $P < 0.001$) at the last follow-up; however, the median daily dose of pyridostigmine bromide did not change statistically (Fig. 1A, $216[180–360]$ vs $159[60–480]$ mg, $P = 0.207$). The combination of pyridostigmine bromide, corticosteroids and immunosuppressants was adopted as the main therapeutic pattern and 16/21 (76.2%) patients received the combination therapy after the onset symptoms. Six patients received calcineurine inhibitors (tacrolimus) combined with pyridostigmine bromide and corticosteroids. Two patients received antimetabolites (azathioprine), however, this application did not have a satisfactory therapeutic effect, and both patients experienced disease progression. One patient used plasma exchange (five times), who underwent onset to myasthenic crisis in 1 month (MGFA V). One patient received IVIg when she suffered a myasthenic crisis. Interestingly, at follow-up three patients adopted Chinese herbal medicine instead of pyridostigmine bromide or corticosteroids. With the maintenance of herbal medicine, the symptoms of the patients were stable for a long time without progression.

Prognosis

Three of the 21 patients were lost to the last follow up. Eighteen MuSK-MG (85.7%) patients had a long-term follow-up with an average time of 1202.17 $\pm$ 976.73 (range 306–3762) days (Table 3). Mean follow-up period of OMG patients was slightly longer (1240.10 $\pm$ 1215.31) compared to the BMG groups (1163.29 $\pm$ 693.86, $P = 0.88$). At the end of the follow-up period, long-term outcomes were generally favorable (Table 3): 1 (4.8%) patient received complete stable remission (CSR), 9 (42.9%) patients were in minimal manifestations (MM), 4 (19.0%) had improved, 1 (4.8%) remained an unchanged condition and 2 (9.5%) patients died during the period. Females predominated in CSR or MM patients (female: male = 8:2). Thirteen (61.9%) patients received long-term therapy with monotherapy or drugs combination (pyridostigmine bromide, corticosteroids and tacrolimus). We noticed that at last follow-up, four patients kept tacrolimus as a maintenance treatment complemented by pyridostigmine bromide or corticosteroids, and all of them (100%) achieved a MGFA-PIS of MM. In this study, one patient treated with long-term acupuncture without taking medication and the effect was unsatisfied. After receiving regular inpatient treatment, two patients adopted herbal medicine as a maintenance therapy and achieved a long-term stable condition.
In recent years, several centers reported the clinical characteristics of MuSK patients (Table 4). These studies have shown that long-term AChE-I treatment in patients with MuSK-MG is first-line treatment in improving symptoms, with an effectiveness rate of 16%-75% in patients with Caucasian MuSK-MG, however there are significant individual differences in these effects[15]. The current study reports suggested that the improvement of symptoms and prognosis in MuSK MG patients depend on early and aggressive treatment and long-term maintenance, and that the combination of drugs is effective in controlling progression and improving symptoms of respiratory muscle weakness[16, 17]. As the most commonly AChE-I agent, pyridostigmine bromide was used in 17/21 (81.0%) MuSK-MG patients in our study, with 10/17 (58.8%) patients showing symptomatic improvement. In this study, 16 patients were treated with corticosteroids in combination with AChE-I in the early stages and 56.3% of patients achieved long-term symptomatic stability or remission according to MGFA post-intervention status. Although 2 patients died of their disease, our experience indicated that, the application of corticosteroids appeared a certain effect on the disease deterioration. Similar results were published by Zhang et al, but Lavrmic et al reported MuSK positive patients in their center were all treated with corticosteroid drugs with a response rate of 47%[6, 18]. Furthermore, according to the drug dose at the last follow-up, low doses of pyridostigmine bromide and corticosteroids seems to be sufficiently for the symptomatic maintaining in MuSK-MG patients.
Table 4

Summary of relevant studies that focused on the clinical features and treatment of MuSKAb-positive patients

| References          | Country   | Date   | Number | Pyridostigmine therapy | CS therapy | Therapy response evaluation | Thymectomy | Follow-up | Status at the end of observation period |
|---------------------|-----------|--------|--------|-------------------------|------------|-----------------------------|-------------|-----------|----------------------------------------|
| Sanders, D B et al.[21] | USA       | 2003   | 12     | 75%                     | ND         | ND                          | ND          | ND        | ND                                     |
| Evoli, Amelia et al.[22] | Italy     | 2003   | 37     | most                    | 81.1%      | MGFA classification         | 40.5%       | At least 1 year | 3 CSR;4 PR;4 MM; 21 improved; 3 unchanged; 2 died |
| Lavnic, D et al.[18]   | Serbia    | 2005   | 17     | most                    | 100%       | ND                          | ND          | Yes       | 11.8%CSR,23.5%PR; 29.4%improved; 23.6%unchanged; 11.7%died |
| Lee, Jee-Young et al.[9] | Korea     | 2006   | 4      | ND                       | 100%       | MGFA classification         | 25%         | ND        | 100%improved                             |
| Ohta, K et al.[6]      | Japan     | 2007   | 23     | ND                       | 52.2%      | MGFA classification         | 13.0%       | ND        | 3 PR; 6 improved; 3 unchanged           |
| Guptill, Jeffrey T et al.[4] | USA     | 2010   | 110    | 98%                     | 92%        | MGFA classification         | 36%         | 11 years for the Rome patient; 5.3 years for the Duke patients | 7.3%CSR;6.4%PR;40.4%MM, 37.6%improved; 7.3%unchanged;0.9%Worse |
| Li, Mingqiang et al.[8] | China     | 2018   | 2      | 100%                    | 100%       | ND                          | 50%         | ND        | 50%MM, 50% improved                     |
| Zhang, Zunwei et al.[10] | China     | 2020   | 14     | 57.1%                   | 100%       | MGFA classification         | ND          | 11.8 ± 11.0 months                      | 7.7%CSR;23.1%PR; 53.8%improved; 15.4%unchanged |

CS, corticosteroids; ND, not described; CSR, complete stable remission; PR, pharmacologic remission; MM, minimal manifestations

In addition, tacrolimus performed in 6 patients and 4/6 patients adopted the drug as a maintain therapy at the last follow up. In consideration of the price and health insurance in local area, no patients in this study received rituximab. Compared with conventional treatment for MG, especially in refractory patients, the efficacy and safety of rituximab showed a probability of a favorable outcome[19]. Interestingly, two patients with a mild onset symptom chose herbal medicine as a long-term maintain therapy during the disease process. One patient received corticosteroids in the progression period, then chose to take herbal medicine when the symptoms were stable. At the last follow up, this patient kept herbal medicine therapy with a minimal manifestations condition and another patient was in complete stable remission. Thymectomy was performed in some MuSK patients (Table 3) and the outcome analyses failed to prove the efficacy of thymectomy for these patients. And the multicenter cohort also indicated thymectomy was not associated with additional clinical improvement of MuSK patients[20]. Although the mediastinum CT scan was examined as a common practice in our center, thymectomy was not recommended.

Most (85.7%) patients in this study had a long term follow-up (range 306–3762 days) and the status at the end of observation period showed a good result compared with previous studied[4, 18]. Two patients were treated with IVig or plasma exchange while experiencing a MG crisis and received satisfied clinical results, suggests the importance of timely and feasible treatment in an urgent condition. Jeffrey et al. confirmed the clinical improvement of IVig and plasma exchange and recommended that, the effect of plasma exchange is rapid and dramatic for acute exacerbations, comparing to IVig[4]. However, two patients died during the period, which reminds these reasons such as elder, combined underlying diseases or physical condition may be factors in their poor prognosis, and classic therapy only has an effect on prolong the prognosis to some extent. The 9.5% mortality reminds MuSK MG is still intractable for physicians. Patients with refractory symptoms and unsatisfied responsive to classical treatment need considerate care and further exploration of effective therapy is urgent.

Conclusions

In summary, our experience from 21 patients described the clinical presentations and long-term outcome of treatment strategy in MuSK-MG. Female patients were more prevalent and the involvement of extraocular muscle occurred as a primary initial episode. However, these patients had a rapid progress to a generalized state. The use of combination treatment is helpful to symptom improvement and clinical outcome. But some patients with MuSK Ab responded poorly to standard care, early introduction of more effective treatment should be considered once a diagnosis was confirmed.

Abbreviations
MG: Myasthenia gravis; AChR: Acetylcholine receptor; MuSK: Muscle-specific tyrosine kinase; MGFA: Myasthenia Gravis Foundation of America; CSR: Complete Stable Remission; PR: Pharmacologic Remission; MM: Minimal Manifestation; OMG: Ocular myasthenia gravis; BMG: Bulbar myasthenia gravis; GMG: Generalized myasthenia gravis; AChE-I: Acetylcholinesterase inhibitor.

Declarations

Acknowledgments
Not applicable.

Author Contributions

SZ and QH designed the study, drafted the manuscript, and contributed to the discussion. QH and FL collected and analyzed the data. SZ reviewed the manuscript. All authors approved the submitted version.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. All methods in this study were performed in accordance with the relevant guidelines and regulations of our ethical files (2020-KY-231). All participants were recruited at the First Affiliated Hospital of Zhengzhou University. Written informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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**Figures**

(A) Pyridostigmine bromide

![Pyridostigmine dose graph](image)

(B) Corticosteroids

![Corticosteroids dose graph](image)

**Figure 1**

Comparison of daily medications of MuSK MG patients between the hospitalization period and at last follow-up. Daily dose of pyridostigmine bromide(A), corticosteroids(B) between the hospitalization period and at last follow-up.