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The Clinical Course and Treatment of a Case of Refractory Systemic Juvenile Myasthenia Gravis Successfully Treated with Thymectomy

Moriei Shibuya,[1,*] Minobu Shichiji,[2,*] Miki Ikeda,[1] Kaori Kodama,[1] Takuya Miyabayashi,[1] Ryo Sato,[1] Yukimune Okubo,[1] Wakaba Endo,[1] Takehiko Inui,[1] Noriko Togashi,[1] Mika Nagao,[3] Kaname Sato,[3] Takatoshi Sato,[2] Masato Kanzaki,[4] Osamu Segawa,[5] Kenta Masui,[6] Keiko Ishigaki[2] and Kazuhiro Haginoya[1]

[1]Department of Pediatric Neurology, Miyagi Children's Hospital, Sendai, Miyagi, Japan
[2]Department of Pediatrics, Tokyo Women's Medical University School of Medicine, Tokyo, Japan
[3]Department of Pediatrics, Ohta Nishinouchi Hospital, Koriyama, Fukushima, Japan
[4]Department of Thoracic Surgery, Tokyo Women's Medical University, Tokyo, Japan
[5]Department of Pediatric Surgery, Tokyo Women's Medical University, Tokyo, Japan
[6]Department of Surgical Pathology, Tokyo Women's Medical University, Tokyo, Japan

Juvenile myasthenia gravis (JMG) exhibits a more favorable response to glucocorticoids and has a better prognosis than adult myasthenia gravis. However, no established treatment exists for refractory JMG. Although thymectomy has been performed in several patients with refractory systemic JMG, there are few detailed clinical descriptions of patients who underwent thymectomy. Here, we present the case of a 10-year-old boy with refractory systemic JMG who was successfully treated with thymectomy. The patient developed symptoms, including dysphagia, malaise, diurnal ptosis, and weakness in the trunk muscles, and he was diagnosed with generalized JMG. Despite undergoing various treatments, including steroids, tacrolimus, steroid pulse therapy, intravenous immunoglobulin, azathioprine (AZT), and rituximab, his symptoms did not improve. Therefore, he underwent a thoracoscopic thymectomy 24 months after disease onset. Thymectomy led to remission, as demonstrated by a significant reduction in the quantitative myasthenia gravis score and anti-acetylcholine receptor antibody levels, which persisted for 43 months after surgery. Our case demonstrates the effectiveness of thymectomy in systemic JMG patients with positive anti-acetylcholine receptor antibodies, despite therapeutic failure with AZT and rituximab, within 2 years of disease onset.

Keywords: anti-AchR antibody; azathioprine; juvenile myasthenia gravis; rituximab; thymectomy
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Introduction

Juvenile myasthenia gravis (JMG) can be a pure ocular myopathy, latent systemic myopathy, or systemic myopathy (Lin et al. 2023). Compared to adults, JMG has a better response to glucocorticoids and a better prognosis, but there is no established treatment for refractory cases. Thymectomy has been performed in some patients with refractory systemic JMG (Ng and Hartley 2021; De Boer et al. 2023). However, there are few detailed clinical descrip-

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*These two authors contributed equally to this study.
Correspondence: Kazuhiro Haginoya, Department of Pediatric Neurology, Miyagi Children's Hospital, 4-3-17 Ochiai, Aoba-ku, Sendai, Miyagi 989-3126, Japan.
e-mail: khaginoya@kha.biglobe.ne.jp
Keiko Ishigaki, Department of Pediatrics, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
e-mail: ishigaki.keiko@twmu.ac.jp

tions of patients who underwent thymectomy. Here, we present a patient with refractory systemic JMG successfully treated with thymectomy.

Case Presentation

A boy was born normally to non-consanguineous Japanese parents after a full-term pregnancy. He presented to a local doctor with dysphagia, malaise, diurnal ptosis, and truncal muscle weakness at 10 years of age. A positive Tensilon test and waning of the M-wave repetition test were evident. Serum anti-acetylcholine receptor (AchR) was positive at 8 nmol/L (reference range: 0-0.3 nmol/L), and anti-MuSK antibody was negative. Thoracic magnetic resonance imaging showed no thymoma. He was diagnosed with systemic myasthenia gravis (MG): MG Foundation of America (MGFA) Clinical Classification IIb (Jaretzki et al. 2000). The patient's quantitative myasthenia gravis (QMG) score (objective functional classification) (Jaretzki et al. 2000) was 13 points.

In the second month after onset, he was started on prednisolone every other day without any improvement and was subsequently treated consecutively with tacrolimus (3 mg/day), and intravenous immunoglobulin (IVIG) (400 mg/kg for 5 days). However, his QMG score and anti-AchR antibody level did not improve. He complained of fatigue, dysphagia, dysarthria, and dysphasia. He was referred to our hospital 3 months after onset.

At the time of our initial examination, his QMG score was 9 points and his anti-AchR antibody level was 9.9 nmol/L. Despite increasing the steroid (prednisolone up to 40 mg/48 h) and tacrolimus (up to 7 mg/day) doses and administering steroid pulse therapy (methylprednisolone 30

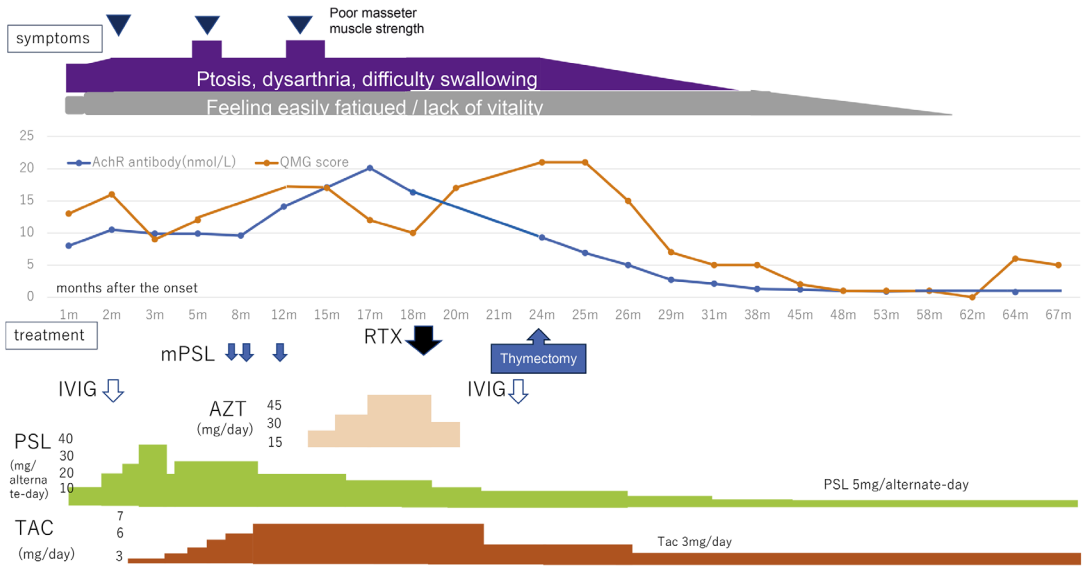

Fig. 1. Clinical course and treatment of the patient.
The patient's symptoms were improved after thymectomy. The anti-AchR antibody titer and QMG score dropped after thymectomy. Even after therapeutic failure with azathioprine and rituximab, thymectomy was effective in this patient. 1-67 m, months 1-67 after disease onset; PSL, prednisolone; TAC, tacrolimus; mPSL, methylprednisolone; IVIG, intravenous immunoglobulin; AZT, azathioprine; RTX, rituximab.

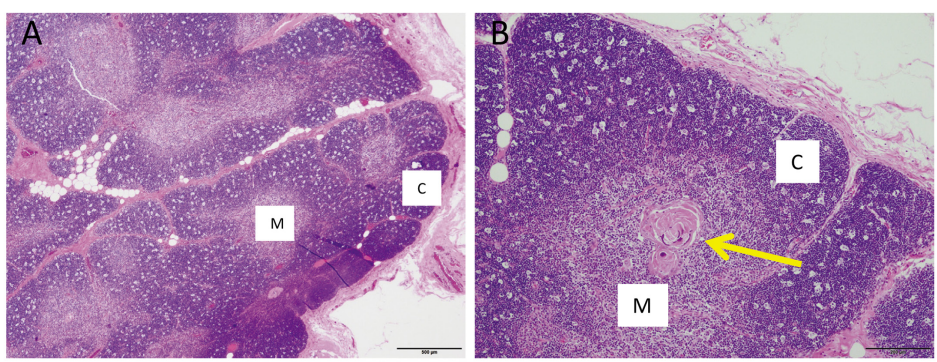

Fig. 2. Histopathological findings of the resected thymus.
The thymus is enlarged with preserved cortex (C) and medulla (M). The medulla contains Hassal corpuscles (arrow). No neoplastic change or lymphoid follicle formation is observed. Hematoxylin and eosin staining. Magnification: (A) × 4, a bar = 500 μm; (B) × 10, a bar = 200 μm.

mg/kg for 3 days at 7, 8, and 12 months after disease onset) and azathioprine (AZT) (15-45 mg/day), no significant improvements were observed in the QMG score and anti-AchR antibody levels, and AZT caused diarrhea. Approximately 18 months after disease onset, rituximab (375 mg/m^2 four times weekly) was administered. However, the response was poor, and the QMG score increased to 17 points.

The patient was transferred for a thymectomy when he had a QMG score of 21 points and anti-AchR antibody level of 9.3 nmol/L. He was treated with IVIG to prevent a perioperative crisis and underwent thoracoscopic thymectomy 1 week later, which was 24 months after disease onset (Fig. 1). He displayed no postoperative crisis symptoms and his dysarthria improved on the 10th postoperative day. When he was discharged from the hospital 2 weeks postoperatively, his anti-AchR antibody level had decreased to 6.9 nmol/L. At 5 months postoperatively, his QMG score had improved to 7 points, and prednisolone was tapered. At 6 months postoperatively, fatigue remained, but dysphagia and dysarthria had disappeared. At 43 months postoperatively, almost all of the patient's symptoms had disappeared and the QMG score had dropped below 6 points. Anti-AchR antibody level decreased to 0.8 nmol/L. The thymus histology showed hyperplasia (Fig. 2).

Discussion

JMG occurs in children younger than 18 years of age; however, its treatment is often based on adult guidelines. Oral prednisolone is recommended as the first-line treatment for systemic JMG, and immunosuppressive drugs such as AZT, rituximab, IVIG maintenance therapy, and plasma exchange are administered as secondary treatments (Munot et al. 2020; Lin et al. 2023). Recent randomized trials examining thymectomy in patients 18-65 years of age who had generalized nonthymomatous myasthenia showed that thymectomy was effective in non-thymoma patients younger than 50 years (Wolfe et al. 2016, 2019). Despite controversy over the optimal time for the operation, thymectomy has been shown to be effective in pediatric patients in several retrospective studies (Tracy et al. 2009; Ng and Hartley 2021; Zhang et al. 2022; De Boer et al. 2023). A review of JMG patients who underwent thymectomy between 1997 and 2020 revealed symptomatic improvement and complete discontinuation of medicines in 77% and 40% of patients, respectively (Ng and Hartley 2021). The age at which thymectomy was performed and the duration of follow-up varied widely across studies. Some studies have indicated that thymectomy in patients as young as 17 months does not appear to impair immunological function (Tracy et al. 2009). Early surgical intervention, intervention after puberty onset, and the presence of anti-AchR antibodies, severe disease, and thymic hyperplasia can be associated with improved surgical outcomes (Ng and Hartley 2021). A recent report found that 32 patients with JMG who underwent thymectomy showed a gradual decrease in postoperative QMG and MG-ADL scores (subjective functional classification), and early intervention within 2 years of onset was associated with better short- and long-term neurological outcomes, especially for patients with systemic MG (Zhang et al. 2022).

In conclusion, even after therapeutic failure with AZT and rituximab, thymectomy may be effective in pediatric patients with systemic MG and positive anti-AchR antibody, within 2 years of disease onset.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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