

Double Seronegative Myasthenia Gravis with Anti-LRP4 Antibodies Presenting with Dropped Head and Acute Respiratory Insufficiency

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Abstract

We herein report the case of a 72-year-old man demonstrating myasthenia gravis (MG) with a dropped head and acute respiratory insufficiency. There was no ocular, bulbar, or limb involvement. The patient was seronegative for anti-acetylcholine receptor (AChR) antibodies and anti-muscle-specific tyrosine kinase (MuSK) antibodies. Subsequent tests showed seropositivity for anti-low-density lipoprotein receptor-related protein 4 (LRP4) antibodies. The addition of steroid pulse therapy resulted in a full remission of his respiratory symptoms. This presentation suggests that LRP4-positive MG should be considered in the differential diagnosis of patients presenting with acute respiratory insufficiency without either cranial or limb involvement.

Key words: myasthenia gravis, anti-LRP4 antibodies, acute respiratory insufficiency, dropped head, steroid pulse therapy

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Introduction

Myasthenia gravis (MG) is an autoimmune syndrome caused by a failure of neuromuscular transmission, which results in variable muscle weakness and is exacerbated by exercise (1). Autoantibodies against the muscle nicotinic acetylcholine receptor (AChR) can be detected in approximately 80-85% of all patients with generalized MG (2, 3) and in approximately 40% of anti-AChR seronegative MG patients who have antibodies against muscle-specific kinase (MuSK) (3, 4). Recently, the novel antigen, the low-density lipoprotein receptor-related protein 4 (LRP4), has been identified as a target for the autoantibodies in MG (5), and anti-LRP4 antibodies were detected in the serum of approximately 2-46% of double seronegative MG (dsMG) patients (3, 5-7). In this report, we present a case of undiagnosed MG with an acute onset of respiratory insufficiency without either ocular or limb involvement. The patient turned anti-LRP4 seropositive and responded positively to

steroid therapy. Our study highlights the fact that making an early diagnosis of such cases can be very difficult.

Case Report

A 72-year-old Japanese man was admitted to our department presenting with an 18-month history of dropped head. His symptoms did not fluctuate over the next few days. A neurological examination revealed mild neck extensor weakness (MMT 4/5), but there were no signs of weakness in the ocular, tongue, facial or limb muscles. His deep tendon reflexes were preserved with no signs of pyramidal involvement. The results of routine blood tests, including those for thyroid function and muscle enzymes, were normal. SpO₂ was 96% on room air.

Seven days after admission, he presented with general fatigue and dyspnea. An arterial blood gas analysis of room air was PaCO₂ 55.9 mmHg and %VC (vital capacity) was 63.7% in spirometry, and he needed noninvasive positive-pressure ventilation (NPPV). A chest computer tomography

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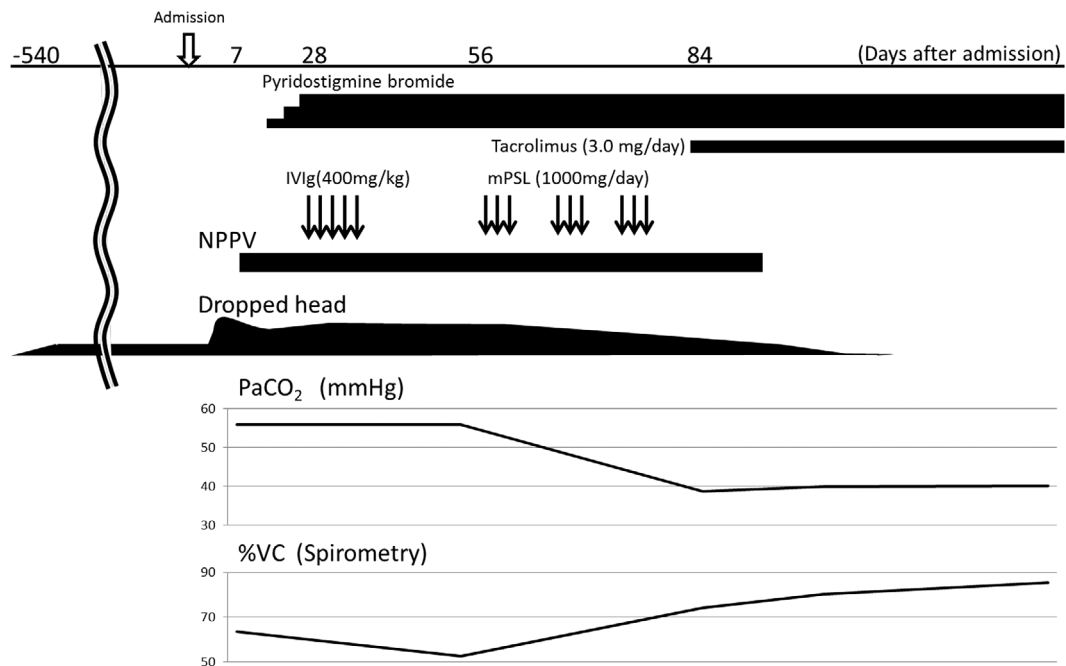


Figure. The patient's clinical course is shown.

(CT) scan showed no definite evidence of either pneumonia or pulmonary thromboembolism. Chest CT also showed no sign of thymoma. No abnormalities were observed on magnetic resonance imaging (MRI) of the brain and cervical spine and cerebrospinal fluid examination. Repetitive nerve stimulation (RNS) studies of the trapezius muscle showed about a 20% decrease in his compound muscle action potential, although RNS studies in the orbicularis oculi and abductor digiti minimi muscles were normal. Nerve conduction studies performed on his right upper and lower limbs were normal. Needle electromyography of the sternocleidomastoid and cervical paraspinal muscles showed a mild, low amplitude of the motor unit potentials. A muscle biopsy from the left biceps brachii muscles showed no significant lesions. The serum anti-AChR antibodies and anti-MuSK antibodies were negative. A subsequent luciferase immunoprecipitation system test revealed seropositivity to anti-LRP4 antibodies.

The administration of an oral cholinesterase inhibitor (pyridostigmine bromide, 60 mg three times daily) or an intravenous immunoglobulin (IVIg, 400 mg/kg \times 5 days) did not alleviate his respiratory symptoms. Two months after admission, steroid pulse therapy (methyl prednisolone 1,000 mg \times 3 days) was started, and his respiratory and neck symptoms and hypercapnia thereafter markedly improved (Figure). We performed the steroid pulse therapy every week for three times, which allowed him to gradually withdraw from the NPPV. Subsequently, he was administered tacrolimus (3.0 mg/day), and he has since remained symptom-free for over 8 months.

Discussion

We present the case of a dsMG patient with anti-LRP4 antibodies without a common phenotype. To the best of our

knowledge, this is the first clinical report of MG with seropositivity for only anti-LRP4 antibodies showing predominantly respiratory symptoms.

Several reports have described the clinical features of MG patients with anti-LRP4 antibodies. Zouvelou et al. reported two cases of dsMG with anti-LRP4 antibodies. One patient presented with isolated neck extensor weakness and the other showed ocular, bulbar and cervical symptoms. Both patients presented with mild symptoms and responded promptly to cholinesterase inhibitor (8). Tsivgoulis et al. reported the clinical presentation of three dsMG patients with anti-LRP4 antibodies who showed isolated ocular symptoms and a good response to treatment with cholinesterase inhibitor and/or corticosteroids (9). Tsivgoulis et al. also described a case of MG presenting with bulbar symptoms and double seropositivity for anti-AChR and anti-LRP4 antibodies; this patient responded to cholinesterase inhibitor and corticosteroids (7). All of these reported cases showed mild symptoms and a good response to the conventional treatments of MG. However, the typical clinical symptoms of MG patients with anti-LRP4 antibodies remain unclear because the number of detailed clinical reports is too small. Our case suggests that MG patients with anti-LRP4 antibodies could show a dropped head as an initial symptom at presentation.

Zisimopoulou et al. studied the clinical data of over 800 MG patients and reported that the majority of dsMG patients with anti-LRP4 antibodies presented with ocular or mild generalized symptoms. They showed a positive response to cholinesterase inhibitors or corticosteroids, which was similar to the clinical features of MG patients with anti-AChR antibodies (10). It was also reported that 6.6% of MG patients with anti-LRP4 antibodies demonstrated myasthenic crisis, and that double seropositive MG patients (especially anti-MuSK and anti-LRP4 antibodies) had more severe

symptoms, such as myasthenic crisis (10). However, no detailed clinical data from each of these patients was reported. Our case suggests that seropositivity for anti-LRP4 antibodies alone (without anti-AChR and/or anti-MuSK antibodies) can induce respiratory symptoms.

In our case, corticosteroid therapy elicited a good response, which was similar to that of the previously reported cases (7, 9). On the other hand, cholinesterase inhibitor therapy was ineffective. As Zisimopoulou et al. indicated, 9.6% of MG patients with anti-LRP4 antibodies did not respond to treatment with cholinesterase inhibitors (10). Moreover, in our case, IVIG was ineffective, whereas tacrolimus was effective and prevented the recurrence of myasthenic symptoms. Zisimopoulou et al. showed that 10 out of 32 MG patients with anti-LRP4 antibodies were treated with IVIG, and 12 out of 28 patients were treated with azathioprine; however, the outcome of these therapies was not described in the paper (10). Further accumulation of clinical data is therefore necessary to understand the effect of IVIG and immunosuppressants on MG patients with anti-LRP4 antibodies.

LRP4 is a member of the low-density lipoprotein receptor family and is known to bind directly to neural agrin (11), which is necessary for the NMJ (neuromuscular junction) formation and neural agrin-induced activation of MuSK and AChR clustering (11-13). Higuchi et al. showed that anti-LRP4 sera from MG inhibited the interaction between LRP4 and neural agrin (5). Shen et al. reported that anti-LRP4 sera decreased cell surface LRP4 levels and inhibited both agrin-induced MuSK activation and AChR clustering (14). They also demonstrated that immunization with the extracellular domain of LRP4 causes muscle weakness in mice (14). Moreover, recent studies in mice show that the loss of muscle LRP4 alone is sufficient to cause myasthenic symptoms (15). On the other hand, because it has been also recently reported that anti-LRP4 antibodies are present in the serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis (ALS) (16), the specificity of the anti-LRP4 antibodies for MG remains controversial (17).

Acute neuromuscular respiratory failure is caused not only by MG, but also by other diseases, such as Guillain-Barré syndrome, myopathies and ALS (18). It is often challenging to diagnose MG at an early phase because it rarely presents as isolated respiratory muscle weakness (19). This presentation suggests that neurologists should consider MG with anti-LRP4 antibodies in the differential diagnosis of patients presenting with unexplained dyspnea.

The authors state that they have no Conflict of Interest (COI).

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References

- Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. *J Clin Invest* **116**: 2843-2854, 2006.
- Richman DP, Agius MA, Kirvan CA, et al. Antibody effector mechanisms in myasthenia gravis. The complement hypothesis. *Ann NY Acad Sci* **841**: 450-465, 1998.
- Zhang B, Tzartos JS, Belimezi M, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. *Arch Neurol* **69**: 445-451, 2012.
- Sanders DB, El-Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. *Neurology* **60**: 1978-1980, 2003.
- Higuchi O, Hamuro J, Motomura M, Yamanashi Y. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. *Ann Neurol* **69**: 418-422, 2011.
- Pevzner A, Schoser B, Peters K, et al. Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis. *J Neurol* **259**: 427-435, 2012.
- Tsivgoulis G, Dervenoulas G, Tzartos SJ, Zompola C, Papa-georgiou SG, Voumvourakis K. Double seropositive myasthenia gravis with acetylcholine receptor and lipoprotein receptor-related protein 4 antibodies. *Muscle Nerve* **49**: 930-931, 2014.
- Zouvelou V, Zisimopoulou P, Rentzos M, et al. Double seronegative myasthenia gravis with anti-LRP 4 antibodies. *Neuromuscul Disord* **23**: 568-570, 2013.
- Tsivgoulis G, Dervenoulas G, Kokotis P, et al. Double seronegative myasthenia gravis with low density lipoprotein-4 (LRP4) antibodies presenting with isolated ocular symptoms. *J Neurol Sci* **346**: 328-330, 2014.
- Zisimopoulou P, Evangelakou P, Tzartos J, et al. A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis. *J Autoimmun* **52**: 139-145, 2014.
- Zhang B, Luo S, Wang Q, Suzuki T, Xiong WC, Mei L. LRP4 serves as a coreceptor of agrin. *Neuron* **60**: 285-297, 2008.
- Weatherbee SD, Anderson KV, Niswander LA. LDL-receptor-related protein 4 is crucial for formation of the neuromuscular junction. *Development* **133**: 4993-5000, 2006.
- Kim N, Stiegler AL, Cameron TO, et al. Lrp4 is a receptor for Agrin and forms a complex with MuSK. *Cell* **135**: 334-342, 2008.
- Shen C, Lu Y, Zhang B, et al. Antibodies against low-density lipoprotein receptor-related protein 4 induce myasthenia gravis. *J Clin Invest* **123**: 5190-5202, 2013.
- Barik A, Lu Y, Sathyamurthy A, et al. LRP4 is critical for neuromuscular junction maintenance. *J Neurosci* **34**: 13892-13905, 2014.
- Tzartos JS, Zisimopoulou P, Rentzos M, et al. LRP4 antibodies in serum and CSF from amyotrophic lateral sclerosis patients. *Ann Clin Transl Neurol* **1**: 80-87, 2014.
- Evoli A, Iorio R. Characteristics of myasthenia gravis with antibodies to muscle-specific kinase and low-density lipoprotein-related receptor protein 4. *Clin Exp Neuroimmunol* **6**: 40-48, 2015.
- Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. *Arch Neurol* **67**: 1089-1094, 2010.
- Mandaliya R, Kulandaivel K, Nowotarski N, Buddhdev K, Patel R. A Challenging diagnosis of fluctuating dyspnea: myasthenia gravis. *J Clin Diagn Res* **9**: OD06-OD08, 2015.

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