CASE REPORT

Anti-MuSK Antibody-positive Myasthenia Gravis Mimicking Amyotrophic Lateral Sclerosis

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Abstract

We herein investigated the clinical features of three patients with anti-muscle-specific tyrosine kinase (MuSK) antibody-positive myasthenia gravis (MG), which was initially difficult to distinguish from amyotrophic lateral sclerosis (ALS). The patients exhibited dropped head syndrome or dysphagia as initial symptoms. Although their clinical findings were compatible with the revised El Escorial Criteria for ALS, their progression appeared to be more rapid than that of ALS. Both the edrophonium and repetitive nerve stimulation tests yielded negative results, and diurnal fluctuation was not confirmed. The patients were ultimately diagnosed with anti-MuSK antibody-positive MG. We therefore recommend the measurement of anti-MuSK antibodies when encountering such cases.

Key words: muscle-specific tyrosine kinase (MuSK), anti-MuSK antibody, amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG), plasmapheresis

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Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by signs and symptoms caused by the degeneration of the upper and lower motor neurons, which leads to the progressive weakness of the bulbar, limb, thoracic, and abdominal muscles (1, 2). Almost half of all ALS patients will die within 3 years of symptom onset, primarily because of respiratory failure (3, 4). A misdiagnosis of ALS, instead of other neurological disorders which can be treated, should be avoided.

Approximately 5-8% of the total number of patients with myasthenia gravis (MG) has antibodies against the muscle-specific tyrosine kinase (MuSK) receptor (5). The patients with anti-MuSK antibody-positive myasthenia gravis (MuSK-MG) exhibit a distinct clinical phenotype and may differ from “typical” MG associated with antibodies against the acetylcholine receptor (AChR) (5, 6). The diagnosis of MuSK-MG is often challenging because of its atypical presentation, with little or no diurnal fluctuation of the myasthenic symptoms, poor response to the edrophonium test, and negative results in the electrodiagnostic studies, including repetitive nerve stimulation (RNS). Bulbar weakness or dropped head syndrome, which is commonly found in both the patients with MuSK-MG and motor neuron disease (MND), may hamper the differential diagnosis of this condition (6).

We herein report three cases ultimately diagnosed as MuSK-MG and whose clinical findings were compatible with the revised El Escorial Criteria for ALS (7).

Case Reports

Case 1

A 73-year-old Japanese woman presented with dropped
She had a history of cervical spondylosis, hypertension, and weakness of neck extensor muscles, dysarthria, and dysphagia. Nine years after the onset of the disease, the patient was admitted to our hospital because of the progressive weakness of neck extensor muscles, dysarthria, and dysphagia. She had a history of cervical spondylosis, hypertension, and hypercholesterolemia. A neurological examination disclosed weakness in the neck extensor, orbicularis oculi, orbicularis oris, and deltoid muscles, with grade 4 manual muscle testing (MMT). Fasciculations were observed in the facial, bilateral biceps brachii, triceps brachii, and quadriceps femoris muscles. There was no evidence of muscle atrophy. Her tendon reflexes were all normal. The Babinski reflex was present bilaterally. Her neurological findings were compatible with the revised El Escorial Criteria for possible ALS (7), although her pyramidal tract signs could have resulted from cervical spondylosis. She did not report a diurnal fluctuation of the motor symptoms. The edrophonium test did not improve her muscle weakness, and RNS at 3 Hz in the right abductor digiti minimi and trapezius muscles did not show decremental responses. The results of the nerve conduction studies (NCS) performed at the bilateral median, ulnar, tibial, peroneal, and sural nerves were all normal. Needle electromyography (EMG) disclosed fasciculation potentials at rest in the bilateral biceps brachii, first dorsal interossei, and quadriceps femoris muscles. Her anti-AChR antibody titer was within the normal range. Chest computed tomography (CT) revealed a normal appearance of the anterior mediastinum, without either any obvious thymoma or thymic hyperplasia.

Seven months later, she developed diplopia, bilateral blepharoptosis, and dyspnea. Repeated RNS at 3 Hz revealed a 10% decrement in the left trapezius muscles. The anti-MuSK antibody titer, as evaluated by a radioimmunoassay, showed a pathological elevation to 10.53 nmol/L (normal level, <0.05 nmol/L). Her forced vital capacity (FVC) was 28.6%, and her quantitative myasthenia gravis (QMG) score was 19. A muscle biopsy was performed at the left biceps brachii muscles. Hematoxylin and Eosin staining showed a mild variability of the fiber diameter and infrequent small angulated fibers (Figure A). Nicotinamide adenine dinucleotide tetrazolium reductase staining showed a mosaic distribution of types 1 and 2 muscle fibers and no fiber-type grouping. (C) Cholinesterase staining using thiocholine revealed an almost normal distribution and amount of motor end-plates (arrowheads). (D) Acetylcholine receptor (AChR) staining using peroxidase-labeled alpha-bungarotoxin revealed that the AChR density was not visibly decreased (arrows). (E) Complement component 3 (C3) staining using peroxidase-labeled anti-C3 antibodies and (F) immunoglobulin G (IgG) staining using peroxidase-labeled Protein A showed no immune complex depositions (C3 and IgG) at the motor end-plates. Bar, 100 μm.

The patient was treated with oral prednisolone, which was increased up to 25 mg daily for 4 weeks, and thereafter was tapered to 22.5 mg daily. She also received seven courses of double filtration plasmapheresis. The patient showed a remarkable improvement after treatment, with an FVC of 74.7% and a QMG score of 5.

Nine years after the onset of the disease, the patient...
showed no exacerbation of the symptoms with a maintenance therapy of prednisolone (8 mg daily) and tacrolimus hydrate (2 mg daily).

**Case 2**

A 62-year-old Japanese woman presented with dysphagia in January 2013. She had no remarkable medical history. Six months later, she was admitted to our hospital due to the development of dysphagia, dysarthria, and dyspnea. She had rapidly lost weight over the previous year (6 kg in 1 year). A neurological examination disclosed weakness in the orbicularis oculi and oris muscles, with grade 4 MMT. There was no evidence of limb weakness. Her tendon reflexes were generally hyperactive, and her jaw reflex was brisk. Muscle atrophy and fasciculations were not observed. The Babinski reflex was absent. Her neurological findings were compatible with the revised El Escorial Criteria for possible ALS (7). She did not report a diurnal fluctuation of the motor symptoms. The edrophonium test and RNS in the right abductor digitii minimi showed negative results. The NCS and EMG findings were normal. Her anti-AChR antibody titer was within the normal range. Furthermore, no thymic abnormalities on chest CT were observed. Although her FVC was normal (102.5%), an arterial blood gas (ABG) analysis on room air showed hypoxemia [partial pressure of oxygen (PaO2), 63.9 mmHg] and hypercapnia [partial pressure of carbon dioxide (PaCO2), 51.2 mmHg]. Her QMG score was 5. The anti-MuSK antibody titer elevated to 23.0 nmol/L (normal, <0.01 nmol/L). According to these findings, the patient was diagnosed with MuSK-MG.

The patient was treated with oral prednisolone, which was increased up to 20 mg daily for 4 weeks, and thereafter was tapered to 17.5 mg daily. She also received three courses of simple plasma exchange. An ABG analysis on room air revealed an improvement, with a PaO2 of 88.9 mmHg and a PaCO2 of 47.5 mmHg. The patient also exhibited an improved QMG score of 3.

One year after the onset of the disease, the patient showed no exacerbation of the symptoms with a maintenance therapy of prednisolone (15 mg daily).

**Case 3**

A 63-year-old Japanese woman presented with dropped head syndrome in April 2013. She had medical histories of autoimmune hepatitis, hypertension, and hypercholesterolemia. Two months later, she was admitted to our hospital with complaints of weakness of the neck extensor muscles, dysphagia, dysarthria, and dyspnea. She had rapidly lost weight over the previous year (10 kg in 1 year). A neurological examination disclosed bilateral blepharoptosis, weakness of the orbicularis oculi and deltoid muscles with grade 4 MMT, atrophy of the tongue, and hyperactive tendon reflexes in the upper extremities. There was no evidence of any muscle atrophy in the limbs. Fasciculations were observed in the left first dorsal interossei muscle. The Babinski reflex was absent. Her neurological findings were compatible with the revised El Escorial Criteria for possible ALS (7). She did not report a diurnal fluctuation of the motor symptoms. The edrophonium test and RNS in the right abductor digitii minimi and thenar muscles showed negative results. The NCS findings were normal. The EMG showed fascillation potentials at rest in the left first dorsal interossei muscle. Her anti-AChR antibody titer was within the normal range. There was no thymic abnormality on chest CT. Her FVC was 55.6%, and her QMG score was 13. The anti-MuSK antibody titer elevated to 18.0 nmol/L (normal, <0.01 nmol/L). According to these findings, the patient was diagnosed with MuSK-MG.

The patient was treated with oral prednisolone, which was increased up to 25 mg daily for 4 weeks, and then tapered to 22.5 mg daily. She also received three courses of simple plasma exchange. The patient showed a remarkable improvement after therapy, with an FVC of 63.6% and a QMG score of 6.

One year after the onset of the disease, the patient showed no exacerbation of the symptoms with a maintenance therapy of prednisolone (15 mg daily).

**Discussion**

In this report, we described three cases of MuSK-MG that were difficult to distinguish clinically from bulbar-onset ALS.

All three patients were female and exhibited an onset of weakness at over 60 years of age. Their neurological findings were all compatible with the revised El Escorial Criteria for possible ALS; however, the progression of their disease appeared to be more rapid than that of ALS. Although all three patients had weakness in the eyelid closure, facial weakness is not classically considered to be a characteristic early symptom of ALS; rather, it is a more common feature of MG (10). Cases 2 and 3 had substantial weight loss, which was potentially caused by dysphagia associated with the disease.

The mild neurogenic changes observed on a muscle biopsy in case 1 may have been caused by her complication of cervical spondylosis or by MuSK-MG itself. The lack of a diurnal fluctuation of the myasthenic symptoms, a positive response to the edrophonium test, and decremental responses of RNS observed in the three cases made it difficult to prioritize MuSK-MG as the most probable candidate diagnosis. A combination therapy of plasmapheresis and high-dose prednisolone was effective in all three cases (Table).

In a previous report, decremental responses of RNS in the orbicularis oculi muscles were more useful than those in the limb muscles of MuSK-MG patients (11). However, decremental responses of RNS can also occur in the denervated muscles of ALS patients (12); therefore, anti-MuSK antibodies must be evaluated for the establishment of an accurate diagnosis.

There appear to be three distinct clinical phenotypes of MuSK-MG: (i) a form with generalized muscle weakness;
The MuSK protein, which is located at the postsynaptic membrane, anchors the C-terminal portion of collagen Q (ColQ), which binds acetylcholinesterase (AChE) at the N terminal (14, 15). AChE stabilization depends on its binding to ColQ (16). The anti-MuSK antibodies interfere with the MuSK-ColQ binding and reduce the AChE activity at the neuromuscular junction, resulting in an increased synaptic acetylcholine concentration (15). As a result, the MuSK antibodies may produce peripheral nerve hyperexcitability, which can cause muscular fasciculation activities (17). In cases 1 and 3 reported in the present study, fasciculations were constantly confirmed in the widespread areas. The generalized presence of fasciculations in these MuSK-MG patients further raised the possibility of a diagnosis of ALS.

As uncharacteristic clinical findings may be associated with negative results in the pharmacological and electrodiagnostic testing, the diagnosis of MuSK-MG may be overlooked or considerably delayed (6). The present cases suggest that MuSK-MG patients can be misdiagnosed as having a bulbar- or proximal-onset type of ALS. Thus, the evaluation of MuSK antibodies plays an important role in the establishment of an accurate and rapid diagnosis, as well as in the decision of a therapeutic strategy.

Table. Clinical Summary of Three Patients with Anti-MuSK Antibody-positive MG Mimicking ALS.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td>Onset of symptom</td>
<td>dropped head</td>
<td>dysphagia</td>
</tr>
<tr>
<td>Onset-to-admission time (months)</td>
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<td>6</td>
</tr>
<tr>
<td>Revised El Escorial Criteria for ALS</td>
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<td>possible</td>
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<tr>
<td>Daily fluctuation</td>
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<td>negative</td>
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<tr>
<td>Edrophonium test</td>
<td>decrement</td>
<td>normal</td>
</tr>
<tr>
<td>Anti-MuSK antibody level (nmol/L)</td>
<td>10.53 (&lt;0.05)</td>
<td>(0.01)</td>
</tr>
<tr>
<td>Apheresis therapy</td>
<td>DFPP</td>
<td>PE</td>
</tr>
<tr>
<td>Initial prednisolone (mg/day)</td>
<td>25</td>
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<tr>
<td>Improvement of the QMG score</td>
<td>19-5</td>
<td>5-3</td>
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<tr>
<td>Complication</td>
<td>cervical spondylosis</td>
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</table>


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References


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