CASE REPORT

A Patient with Fulminant Myasthenia Gravis Is Seropositive for Both AChR and LRP4 Antibodies, Complicated by Autoimmune Polyglandular Syndrome Type 3

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Abstract:
This article describes the first reported case of myasthenia gravis (MG) seropositive for both acetylcholine receptor antibody and low-density lipoprotein receptor-related protein 4 antibody, complicated by autoimmune polyglandular syndrome (APS) type 3. The patient exhibited myasthenic weakness restricted to the ocular muscles and ptosis. Severe clinical deterioration ensued with predominant bulbar symptoms. MG rapidly worsened, the patient was intubated, and agranulocytosis due to thiamazole was also present, so it was necessary to perform thyroidectomy with tracheostomy and thymectomy in two phases. Both the double-seropositive MG and the APS were involved in the patient’s rapid deterioration.

Key words: acetylcholine receptor, autoimmune polyglandular syndrome, low-density lipoprotein receptor, myasthenia gravis

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Introduction
Myasthenia gravis (MG) is an organ-specific autoimmune disease that affects postsynaptic receptors at neuromuscular junctions. Approximately 80% of patients with MG have antibodies against acetylcholine receptor (AChR), and approximately 4% of patients with MG have antibodies against muscle-specific kinase (MuSK). Low-density lipoprotein receptor-associated protein 4 (LRP4) antibodies have recently been identified as another pathogenic antibody in MG and are reportedly present in approximately 2% of patients (1, 2). Double-seropositive MG patients with AChR antibodies and LRP4 antibodies have rarely been reported. These patients have frequently presented with bulbar symptoms (e.g. dysphagia, aspiration of liquids, dysphonia, or difficulty chewing) (3-7), and none of them have had concomitant autoimmune polyglandular syndrome (APS).

APS, also called polyglandular autoimmune syndrome, was first described by Neufeld in 1980 (8). Based on the types of autoimmune diseases that coexist, it has been classified as APS types 1 to 4. APS type 3 is associated with autoimmune thyroid disease and other autoimmune diseases along with an absence of Addison’s disease, and it is reportedly the most common type in Japan (9).

In this case study, we describe an MG patient with AChR antibodies, LRP4 antibodies, and concomitant APS.

Case Report
The patient was a 37-year-old man with type 1 diabetes who has been treated with insulin self-injection since 3 years of age. His HbA1c had been in the range of 9-10%, and he had begun retinal photocoagulation for proliferative diabetic retinopathy at 26 years of age. Two months prior to the presentation, he had no symptoms; however, he had a
high alkaline phosphatase (ALP) level and measured thyroid function along with hyperthyroidism. He was subsequently diagnosed with Graves’ disease. Left eye ptosis and diplopia had occurred one month prior to the current presentation and had gradually deteriorated. At the patient’s first visit, he was diagnosed with diabetic oculomotor nerve palsy. After two weeks, his diplopia and ptosis had worsened and became bilateral.

On a physical examination, his blood pressure was 116/68 mmHg, and his pulse was 105 beats/min with regular slight tachycardia. A neurological examination revealed severe ptosis in the left eye and mild ptosis in the right eye. The left eye movement was fixed in the middle. The right eye exhibited limitation of adduction and abduction. There was no pupil abnormality or eye protrusion. Tendon reflexes were absent in the upper and lower limbs, but muscle strength in the face was normal, with waning in the musculus orbicularis oculi.

The patient’s initial ocular symptoms were treated with orally administered ambenonium and naphazoline eye drops. Within approximately two weeks, bulbar symptoms, such as dysphagia and shortness of breath, developed. At that time, AChR antibody significantly increased to 10.8 nmol/L, and thiamazole was added to the treatment with intravenous immunoglobulin (IVIg at 400 mg/kg/day for 5 days) was started. Although thiamazole was added for Graves’ disease, he developed a fever and agranulocytosis, and thiamazole was discontinued. He was subsequently determined to be weakly positive for AChR antibody (0.9 nmol/L; cut-off <0.3) and negative for all ganglioside GQ1b antibodies. His ptosis responded markedly on a tensilon test, and MG was diagnosed. On a repetitive stimulation test, the mitral muscle and abductor digiti minimi were normal, but there was waning in the muscles of the orbital region.

The condition was classified as Myasthenia Gravis Foundation of America V.

Intravenous methylprednisolone pulse (1,000 mg for 3 days) and additional IVIg were administered, and his symptoms gradually improved. Thymic hyperplasia was noted on computed tomography, and thymectomy was planned. Because agranulocytosis was caused by thiamazole, however, total thyroidectomy was also necessary. First, the patient un-

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**Table 1. Laboratory Findings.**

| Test         | Value  | Test         | Value  |
|--------------|--------|--------------|--------|
| WBC          | 6,820 μL | HbA1c        | 11.3%  |
| RBC          | 540x10⁶ μL | Free T₁    | 8.5 mg/dL |
| Hb           | 15.7 g/dL | Free T₁    | 2.5 mg/dL |
| Pt           | 17.3x10⁴ μL | TSH        | 0.0 μU/mL |
| CRP          | 0.1 mg/dL | Thyroglobulin| 81.20 ng/mL |
| ALP          | 739 IU/mL | Cortisol    | 6.3 μg/dL |
| AST          | 20 U/L   | ACTH        | 15.9 pg/mL |
| ALT          | 26 U/L   |             |         |
| BUN          | 12.6 mg/dL |            |         |
| Cre          | 0.55 mg/dL |            |         |
| Na           | 139 mEq/L | CSF         |         |
| K            | 4.5 mEq/L | Cell count  | 2 /μL (Lym 100%) |
| Cl           | 105 mEq/L | Protein     | 51 mg/dL |
| Ca           | 9.3 mEq/L | Glucose     | 126 mg/dL |
| Hb           | 15.7 g/dL |             |         |
| TSH-R ab     | 27.9     | TPO ab      | 129.0 IU/mL |
| Tg Ab        | <1.00     |             |         |
| AChR ab      | 0.9 nmol/L |            |         |
| Musk ab      | <0.02 nmol/L |            |         |
| LRP4 ab      | 1.81 AI   |             |         |
| HLA          |          |             |         |
| DQB1*08:02  |          |             |         |
| DQB1*03:02  |          |             |         |
| DRB1*03:02  |          |             |         |
| DRB1*04:06  |          |             |         |

AChR: acetylcholine receptor, ACTH: adrenocorticotropic hormone, ALT: alanine aminotransferase, AST: aspartate transaminase, BUN: blood urea nitrogen, Cre: Creatinine, CSF: cerebrospinal fluid, eGFR: estimated glomerular filtration rate, GAD: glutamic acid decarboxylase, Hb: hemoglobin, HLA: human leukocyte antigen, LRP4: low-density lipoprotein receptor-associated protein 4, Musk: muscle-specific kinase, Tg: thyroglobulin, TPO: thyroid peroxidase, TSH: thyroid-stimulating hormone
derwent thyroidectomy and tracheostomy. One month later, thoracoscopic extended thymectomy was performed. There was no exacerbation during the perioperative period, and we performed tracheostomy closure. Regarding the thymic pathology, thymic tissue with Hassall bodies was observed in islands. There was no thymoma. The AChR antibody titer increased from 0.9 to 10.8 nmol/L and then decreased to 0.5 nmol/L, consistent with the clinical course. The LRP4 antibody titer was highest at the time of the onset of eye movement disorder alone (antibody index 1.81) and then decreased over time (Figure).

**Discussion**

Double-seropositivity for AChR and LRP4 antibodies is rare. Furthermore, it has been reported that only 0.2% of AChR-positive MG cases in China (3) and 7.5% of those in Europe (4) were also positive for LRP4. It is possible that there are differences between races, or that there are more hidden cases that have not actually been measured. There have been a few case reports of AChR/LRP4-positive MG (5-7) but none with APS complications. MG patients with LRP4 antibodies who are negative for AChR and MuSK antibodies usually have mild ocular myasthenic symptoms. Clinical data derived from previously reported patients with AChR/LRP4-positive MG indicate that most are Myasthenia Gravis Foundation of America III or worse, initially exhibiting bulbar symptoms or ocular symptoms followed by bulbar symptoms (3-7).

The weakness observed in the present patient was restricted to ocular muscles in the early period, and then severe bulbar weakness occurred later. The changes in clinical symptoms were relatively acute. We thought that the change in clinical course might have been associated with double-seropositivity for relevant antibodies. The LRP4 titer was high and gradually decreased from the onset. The AChR titer, by contrast, was initially low and then increased as the symptoms worsened. The initial levels of LRP4 antibody mainly caused ocular symptoms, but as the AChR titer rapidly increased, the symptoms rapidly worsened, and the patient developed myasthenic crisis. In MG patients, who are known to be positive for AChR, especially those with sudden changes in symptoms or concomitant APS, as in this case, testing for LRP4 antibody should be considered. The presence of both antibodies is rare, but it is important to also test for LRP4 antibodies even in patients who are known to be positive for AChR antibodies, as their condition may become more severe.

Factors affecting conversion from ocular MG to generalized MG are still debatable (10). The presence of an additional autoimmune disease was reportedly associated with a markedly higher risk of exacerbation and emergency treatment (11). The current patient had several additional autoantibodies related to APS, and this may have contributed to the aggravation of his condition.

MG is well known to be associated with various autoimmune diseases. Cases of MG associated with thyroid diseases (Hashimoto’s disease and Graves’ disease), rheumatoid arthritis, systemic lupus erythematosus, and insulin-dependent diabetes mellitus have also been described (12). There have been several reports of MG and APS (13-19). Six of eight patients had bulbar symptoms that tended to be
severe, and three were intubated. Patients are often young to middle-aged, and thymoma has never been reported, but thymic hyperplasia tends to be slightly more common (Table 2). To our knowledge, the current report is the first to describe a case of double-seropositive MG in conjunction with APS. Since it is not common to report LRP4 titers, double-positive patients may have gone undiagnosed in MG cases with APS.

HLA typing revealed the presence of the DRB1*08:02-DQB1*03:02 haplotype, which is associated with susceptibility to type 1 diabetes mellitus in the Japanese population (20). DRB1*13:02-DQB1*06:04 is also associated with susceptibility to “childhood” MG in the Japanese population (21). That same haplotype was present in a case report of an adult patient with APS type 3 and MG (14). Although the associations between LRP4 antibody and HLA are unclear, these HLA haplotypes may have been involved in the onset of symptoms in the present case.

Three considerations are pertinent with regard to surgical treatment. First, near-emergent thyroidectomy is required for Graves’ disease in cases involving the development of agranulocytosis with thiamazole (22). Second, if tracheostomy is performed, it should be done at the same time as thyroidectomy. Finally, thymectomy is preferred for thymic hyperplasia of early-onset MG (23). It was initially considered for this patient but decided against because the risks of wound infection and fatal mediastinitis due to simultaneous tracheostomy, thyroidectomy, and thymectomy were extremely high. Therefore, thyroidectomy with tracheostomy was later followed by thymectomy.

In the present case, the treatment of MG was complicated by APS. It was initially very difficult to distinguish MG from diabetic ophthalmoplegia or Miller Fisher syndrome because the patient had had type 1 diabetes for more than 30 years. In addition, the combination of Graves’ disease and agranulocytosis due to thiamazole required thyroidec
tomy, which rendered the treatment of MG crisis more complex. Furthermore, the presence of another autoimmune disease may have aggravated MG.

Conclusion

The current case is the first reported one of APS with MG with both AChR and LRP4 antibodies. We surmised that AChR and LRP4 double-seropositivity along with APS both contributed to the aggravation of the patient’s condition. It is necessary to test for LRP4 antibody even in patients who are known to be positive for AChR antibody, as double antibody positivity may cause their condition to become severe.

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

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Table 2. Characteristics of the Present and Previously Reported Patients with MG with APS.

| APS type | Sex | Age | MG related antibody | Symptoms | Thymus gland |
|----------|-----|-----|---------------------|----------|--------------|
|          |     |     | AChR | MuSK | LRP4 | dysphagia, dysarthria, fatigue | Thymectomy Follicular hyperplasia |
| 13 APS3  | Female | 15 | + | NS | NS | Thymectomy Follicular hyperplasia |
| 14 APS3  | Female | 30s | + | NS | NS | Thymectomy Hyperplasia |
| 15 APS3  | Female | 51 | + | NS | NS | Thymectomy Lymphoid follicular hyperplasia |
| 16 APS3  | Female | 51 | - | NS | NS | Thymectomy Follicular hyperplasia |
| 17 APS3  | Male | 14 months | - | + | NS | Treated with radiotherapy because of Thymus hyperplasia at 2 years old. |
| 18 APS2  | Female | 74 | + | NS | NS | Thymectomy Follicular hyperplasia |
| 19 APS3  | Male | 37 | - | Not evaluated | NS | Thymectomy Follicular hyperplasia |
| Our case | APS3 | Male | 37 | + | - | Treated with radiotherapy because of Thymus hyperplasia at 2 years old. |

AChR: acetylcholine receptor, APS: autoimmune polyglandular syndrome, CT: computerized tomography, LRP4: low-density lipoprotein receptor-associated protein 4, MG: myasthenia gravis, MuSK: muscle-specific kinase

NS: not stated
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