□ CASE REPORT □

An Ocular Form of Myasthenia Gravis with a High Titer of Anti-MuSK Antibodies during a Long-term Follow-up

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Abstract

We herein report a case of ocular myasthenia gravis (MG) that was highly positive for anti-muscle-specific tyrosine kinase (MuSK) antibodies. The examined patient exhibited bilateral ptosis and lateral gaze palsy without any generalized symptoms and was diagnosed with ocular MG with anti-MuSK antibodies. She responded to treatment with prednisolone and immunosuppressants and experienced only ocular symptoms for four years and eight months after onset. Ocular MG with anti-MuSK antibodies lasting for a long term has rarely been described. Our findings suggest that it may be reasonable to test for the presence of anti-MuSK antibodies in patients who present with external ophthalmoplegia.

Key words: myasthenia gravis, ocular form, anti-MuSK antibodies, autoimmune disease, long-term

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Introduction

The autoimmune mechanism of myasthenia gravis (MG) was established in 1976 (1). It has been found that 85% of MG patients are positive for anti-acetylcholine receptor (AChR) antibodies (AChR-MG), and up to 50% of patients with ocular MG have detectable levels of anti-AChR antibodies (2). Recently, antibodies against muscle-specific tyrosine kinase (MuSK) were reported to be present in 38-70% of patients with seronegative generalized MG (3-5). Anti-MuSK antibody-positive MG (MuSK-MG) tends to be more severe and more focused in the facio-bulbar area than AChR-MG. The present report describes a case of "ocular" MG and anti-MuSK antibodies lasting over four and a half years.

Case Report

A 33-year-old, right-handed woman developed intermittent diplopia. She was examined by an ophthalmologist; however, no restrictions of eye movement or any other symptoms were revealed. MRI of the brain showed no abnormalities. Two weeks later, the patient's symptoms sponta-

neously improved. After the diplopia repeated two, seven and 19 months later, she was evaluated by a neurologist and was thereafter admitted to our hospital. A neurological examination revealed bilateral ptosis with fatigability and fluctuations over the course of a day. The patient had subjective diplopia, and her extraocular movements presented as lateral gaze palsy. She had no facial or jaw weakness, and she had full strength throughout the neck and limbs. However, because detecting weakness in the orbicularis oculi muscle is difficult, the presence of undetectable weakness cannot be excluded. The patient's deep tendon reflexes and sensation were normal. Thyroid function, the erythrocyte sedimentation rate, tests for rheumatoid factor and the creatine kinase levels were normal. An anti-nuclear antibody titer was negative. An anti-AChR antibody titer was within the normal range. The anti-MuSK antibody titer was determined using radioimmunoassay and the concentration measured 106.0 nM, clearly higher than the cutoff value (0.01 nM) (6). Repetitive nerve stimulation at 5 Hz revealed a 27% decrement of the left orbicularis oculi; however, the test did not show any decrease in the deltoid muscle. The patient was diagnosed to have ocular form-MG with anti-MuSK antibodies. The administration of i.v. edrophonium was positive for repetitive nerve stimulation and the symptoms of diplopia. A

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Table. Summary of Cases with Ocular MG and Anti-MuSK Antibodies

	Caress, 2005	Bennett, 2006	Hanisch, 2006	Chan, 2007	our case
Age (at onset)	18	21	55	37	33
Gender	F	F	F	M	F
disease duration	?	?	3.7 years	14.5 years	4.7 years
edrophonium test	not examined	negative	negative	not examined	positive
titer of anti-MuSK antibodies	31,435 pg/mL	positive	1:13	32,693 pg/mL	106.0 nM
pyridostigmine	stopped by side effect	not effective	used	used	effective
prednisolone (initial)	40 mg/day	10 mg/ day	not used	used	30 mg/day
immunosuppressant	not used		azathioprine	not used	tacrolimus
thymectomy	not done	not done	not done	done	not done
others				ocular muscle atrophy	

CT scan of the patient's chest with contrast enhancement revealed a normal thymus gland without thymoma. The forced vital capacity was 110% and the quantitative myasthenia gravis (QMG) score was 6 with spontaneous double vision and ptosis.

First, the patient was given 120 mg of pyridostigmine/day and 1 mg of atropine/day. This medication proved to be effective for the diplopia; however, the patient was unable to continue taking the medicine due to fasciculation of the facial muscles and diarrhea. Then, at two years from the onset of the disease, the patient was started on prednisolone at a dose of 5 mg/day p.o. that was gradually increased. One month later, the dose was increased to 30 mg/day, and a complete improvement was observed in the diplopia and ptosis. After four weeks of 30 mg of daily prednisolone, the dose was gradually tapered down to 12.5 mg/day; however, the diplopia became slightly recurrent, and after three years from the onset of symptoms, 3 mg of daily tacrolimus was added. Following this, the patient's diplopia and ptosis were under good control without any exacerbation, and the titer of anti-MuSK antibodies decreased to 47.0 nM. The dose of prednisolone was then decreased to 5 mg daily. The patient underwent careful neurological examinations and an electrophysiological test after four and a half years from the onset of symptoms. She showed no generalization. Her symptoms were under good control without the occurrence of myasthenia or ocular symptoms after four years and eight months from the onset of the disease.

Discussion

We herein report a rare case involving purely ocular symptoms that was positive for anti-MuSK antibodies over a long-term follow-up period. Approximately 80-90% of patients with MG are positive for anti-AChR antibodies, and 39-49% of Italian and American (7) and 27% of Japanese (6) seronegative patients have antibodies against MuSK.

Recently, Guptill et al. reported that 39% of 110 MuSK patients had only ocular symptoms at onset, although none exhibited only purely ocular symptoms throughout their clinical course (7). The patients usually progressed to generalized disease within two to three weeks; however, in some

patients, fluctuating ptosis and diplopia remained the only complaint for up to 48 months before bulbar and/or neck weakness occurred. Only four cases of MuSK-MG involving ocular muscles have been reported (Table) (8-11). Two of these involved observation for short terms of less than three to four months (8, 9) and had the potential for generalization later. The other two cases involved observation for longer terms (10, 11). Hanisch et al. reported a patient with only ocular symptoms who was diagnosed with MuSK-MG two years after onset and showed only ocular symptoms for 20 months after the initiation of treatment with azathioprine and pyridostigmine (10). Chan et al. reported a patient with only ocular symptoms who was diagnosed 12 years after onset (11). In that case, ocular MRI revealed ocular muscle atrophy. The patient showed ocular symptoms for two and half years after treatment with thymectomy, prednisolone and pyridostigmine. The latter case involved an approximately 15-year duration of limited ocular motility that did not improve with medication or thymectomy. In that case, other diseases were not adequately excluded. Our patient continued to have ocular symptoms without progression to generalization for more than four and a half years. MuSK-MG with only ocular symptoms occurring over a long term is very rare. In our case, treatment with immunosuppressants, such as prednisolone and tacrolimus, and pyridostigmine was able to prevent progression.

Disease severity and the antibody level are strongly correlated in patients with MuSK-MG (6). Although, in our case, the titer of serum anti-MuSK antibodies decreased under corticosteroid therapy, corresponding with an improvement in the patient's symptoms, the initial titer of anti-MuSK antibodies was extremely high, similar to that observed in the other ocular cases (8, 9).

MuSK-MG has been suggested to have three clinical presentations: indistinguishable from generalized AChR-MG, severe oculobulbar weakness and weakness of the neck, shoulders and respiratory muscles with delayed ocular involvement (3). Our patient might therefore be at risk for developing a subsequent generalization of MG and should therefore be carefully observed in the future because there is no adequate evidence to indicate that immunosuppressive therapy reduces the probability of a progression to generalized MG (12). Although ocular involvement is a rare presentation

of MuSK-MG, it may be reasonable to examine individuals for the presence of anti-MuSK antibodies in any patient who presents with external ophthalmoplegia. Early treatment and care may therefore prevent the risk of a sudden worsening of critical symptoms.

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

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