BRIEF COMMUNICATION

Clinical Characteristics of MuSK Antibody-positive Myasthenia Gravis in Taiwan

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Circulating antibodies of the acetylcholine receptor (AchRAb) are detectable in most patients with generalized myasthenia gravis (MG). A newly discovered antibody against muscle-specific kinase (MuSKAb) has been detected in 40–70% of AchRAb-negative MG patients. We report a series of Taiwanese MuSKAb-positive patients, and compare their clinical features with MuSKAb-negative patients and also with MuSKAb-positive Caucasians. Five out of 44 seronegative generalized MG patients (11.4%) were positive for MuSKAb. Patients with MuSKAb tended to have severe disability and bulbar involvement, and more often experienced crisis or impending crisis. Although all of these patients showed an initial response to immunosuppressant therapy, they had greater disability at follow-up. The clinical features of Taiwanese MuSKAb-positive patients were not different from those of Caucasians, except for a lower prevalence. [*J Formos Med Assoc* 2008;107(7):572–575]

Key Words: autoantibodies, immunotherapy, MuSK protein, myasthenia gravis, plasmapheresis

Myasthenia gravis (MG) is an autoimmune disease that affects neuromuscular transmission and results in muscular weakness. Autoantibodies to acetylcholine receptors (AchRAb) are detected in the sera of 80–90% of patients with generalized MG.[1] However, the sera of around 40% of ocular MG patients and around 10% of generalized MG patients have no AchRAb: such cases are termed seronegative MG (SNMG). Clinical and experimental evidence indicates that SNMG is nevertheless caused by serum factors.[2,3]

Hoch et al first reported a serum IgG antibody against the muscle-specific kinase (MuSKAb) causing clinical weakness in SNMG patients.[4] In the past, MuSKAb has been detected in 40–70% of Caucasian SNMG patients.[4–9] It is reported that the MuSKAb-positive patients are more often women, younger at the onset of MG, have predominant cranial and bulbar muscle weakness and a higher frequency of respiratory failure than the MuSKAb-negative patients.[5] Although these patients may respond to immunotherapy and plasma exchange, they tend to have residual facial and bulbar weakness.

There are only a few reports of MG patients with MuSKAb in Asia. Ohta et al[10] found that seven out of 17 (41%) and Nemoto et al[11] found that four out of 13 (31%) generalized SNMG patients had MuSKAb in Japan. The prevalence and clinical features of MuSKAb were similar to those of Caucasians. In contrast, we reported a very low percentage of MuSKAb (4%) in 26 Taiwanese SNMG patients.[12] There are distinct differences between Chinese and Caucasian MG patients in terms of clinical features and association with human leukocyte antigen.[13,14] For MuSKAb-positive MG

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patients, such racial differences may still exist. Here, we describe and compare clinical characteristics in a series of Taiwanese MuSKAb positive and negative SNMG patients.

Methods

This study comprised 44 consecutive generalized SNMG patients, 12 males and 32 females, aged 3–73 years. Diagnosis was based on typical clinical features and a positive pharmacologic response to oral pyridostigmine or corticosteroids, and was confirmed by electrodiagnostic tests. Patients with other autoimmune diseases or an uncertain clinical course were excluded. All patients were negative for AchRAb using a standard radioimmunoprecipitation assay.

All patients received anticholinesterase therapy. Eighteen of these patients had received immunosuppressants, including a corticosteroid or azathioprine, and 16 patients had undergone thymectomy. The thymic pathology included hyperplasia in 12 patients, atrophy in three patients, and thymoma in one patient. Thirteen patients received plasmapheresis for myasthenic crisis. The clinical status was evaluated according to the MGFA (Myasthenia Gravis Foundation of America) clinical classification.[15]

Each patient gave informed consent. The ethical committee of Shin-Kong Wu Ho-Su Memorial Hospital approved this study.

MuSK antibody assay

MuSK antibodies were detected by standard radioimmunoprecipitation (RSR Ltd., Cardiff, UK). Five μL of serum was incubated with 50 μL of ^{125}I-MuSK for 4 hours. Further immunoprecipitation was done with 50 μL of sheep antihuman immunoglobulin G for 1 hour. Pellets were counted on a gamma counter. Serial dilutions were tested for all MuSKAb-positive samples.

Statistical analysis

We compared clinical features, disease progression, response to treatment, and residual symptoms between MuSKAb-positive and MuSKAb-negative patients. Differences were compared by the χ^2 test for categorical variables or by two-sample *t* tests for continuous variables.

Results

Four women and one man out of 44 SNMG patients (11.4%) had anti-MuSKAb. Four patients suffered from respiratory or pharyngeal muscles weakness, and one patient presented with mainly ocular symptoms. The four patients all had suffered from MG crisis, necessitating plasmapheresis and long-term immunotherapy. One patient received thymectomy for thymus hypertrophy on mediastinum CT. The pathology was thymus hyperplasia.

Females predominated in both MuSKAb-positive (4/5) and MuSKAb-negative groups (28/39). Mean age of onset was slightly older in the MuSKAb-positive group (48.6 ± 13.5 years) compared to the MuSKAb-negative group (34.6 ± 16.8 years) ($p = 0.05$). In contrast to MuSKAb-negative patients whose presentation at disease onset varied widely, MuSKAb-positive patients had exclusively ocular symptoms at onset. However, as disease progressed, 4/5 (80%) patients had maximum disability (MGFA ≥ 3) and 5/5 (100%) MuSkAb-positive patient had bulbar symptoms. MuSKAb-positive patients had more severe disability ($p = 0.003$) and bulbar involvement ($p = 0.05$). Four MuSKAb-positive patients experiencing crisis or impending crisis received plasmapheresis ($p = 0.005$). Although MuSKAb-positive patients showed an initial response to immunosuppressant therapy, they had greater disability (MGFA classification ≥ 3) at follow-up ($p = 0.004$; Table 1).

Discussion

In this Taiwanese SNMG series, the prevalence of MuSKAb (11.4%) was lower than in Caucasian patients. There are wide variations in the prevalence of MuSKAb among different ethnic groups

Table 1. Clinical characteristics of MuSK antibody (MuSKAb)-negative and MuSKAb-positive patients with generalized myasthenia gravis without acetylcholine receptor antibodies in serum

	MuSKAb-negative ($n=39$)	MuSKAb-positive ($n=5$)	p
Female gender	28/39 (71.8%)	4/5 (80%)	NS
Onset age (yr)	34.6 ± 16.8	48.6 ± 13.5	0.0499
Ocular onset	19/39 (48.7%)	5/5 (100%)	NS
Bulbar onset	12/39 (30.8%)	0/5 (0%)	NS
Bulbar symptoms during course	21/39 (58.9%)	5/5 (100%)	0.0481
Bulbar symptoms at last visit	9/39 (23.1%)	3/5 (60%)	NS
Maximum disability (MGFA ≥ 3)	7/39 (18%)	4/5 (80%)	0.0026
Plasmapheresis	8/39 (20.5%)	4/5 (80%)	0.0049
Immunotherapy	14/39 (35.9%)	4/5 (80%)	NS
Thymectomy	15/39 (38.5%)	1/5 (20%)	NS
Improvement after treatment	26/39 (66.7%)	5/5 (100%)	NS

NS = not significant; MGFA = Myasthenia Gravis Foundation of America clinical classification.

Table 2. Clinical characteristics of MuSKAb-positive patients, with generalized myasthenia gravis without acetylcholine receptor antibodies in serum, compared to earlier reports

	Author/Country				
	This study/ Taiwan	Evoli et al[5]/ Italy	Sanders et al[7]/ USA	Lavrnic et al[9]/ Serbia	Nemoto et al[11]/ Japan
MuSKAb prevalence	5/44 (11%)	37/78 (47%)	12/32 (38%)	17/55 (31%)	4/13 (31%)
Female (%)	80	78	100	88	100
Mean age of onset (yr)	48.6	35	38.4	35.6	33
Ocular onset	5/5 (100%)	ND	5/12 (42%)	11/17 (65%)	ND
Bulbar onset	0/5 (0%)	ND	5/12 (42%)	12/17 (71%)	ND
Bulbar symptoms during course	5/5 (100%)	37/37 (100%)	11/12 (92%)	14/17 (83%)	3/4 (75%)
Plasmapheresis or intravenous immunoglobulin	4/5 (80%)	29/37 (78%)	10/12 (83%)	6/17 (35%)	ND
Immunotherapy	4/5 (80%)	35/37 (95%)	12/12 (100%)	17/17 (100%)	4/4 (100%)
Thymectomy	1/5 (20%)	15/37 (41%)	7/12 (58%)	9/17 (53%)	4/4 (100%)
Improvement after treatment	5/5 (100%)	32/37 (87%)	12/12 (100%)	16/17 (94%)	ND

ND = not described.

(Table 2).[4–11,15] In most large studies in Caucasians, the prevalence was generally around 30–40%; however, it varied from as low as 5% among Swedes up to 47% among Italians. In Asians, Ohta et al reported 41% MuSKAb-positivity among Japanese SNMG patients,[10] and Lee et al reported 26.7% MuSKAb-positivity among Koreans.[16] Because the patient numbers of these studies were relatively small, it is difficult to estimate the true prevalence.

Similar to previous studies, we found that MuSKAb-positive patients were predominantly female. Although Evoli et al[5] reported a younger age of onset in the MuSK-positive patients, the Japanese group found no such age difference.[11] Most of the large series reported an onset age of approximately 35 years. In contrast, the age at onset of our MuSKAb-positive patients (48.6 ± 13.5) was later than in our MuSKAb-negative patients (34.6 ± 16.8) or of MuSKAb-positive patients from other series.

MuSKAb-positive patients are more likely to have ocular and bulbar weakness,[3–6] but isolated bulbar or neck muscle weakness has also been

reported.[7] There was no significant difference in the patterns of muscle involvement and severity of disease at disease onset in our series. However, as disease progressed, patients with MuSKAb had more bulbar involvement and more severe weakness. They more often needed plasmapheresis or intravenous immunoglobulin and subsequent long-term immunotherapy. As compared to other series, our patients had exclusively ocular onset; the clinical presentations and disease course were nevertheless similar. All patients showed a beneficial response to immunotherapy.

In summary, our patients had mainly cranial and bulbar muscle involvement, a high frequency of respiratory failure, and relatively mild limb weakness. The clinical features of Taiwanese MuSKAb-positive patients were similar to those of Caucasian patients except for a lower prevalence.

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