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Clinical and Electrophysiologic Responses to Acetylcholinesterase Inhibitors in MuSK-Antibody-Positive Myasthenia Gravis: Evidence for Cholinergic Neuromuscular Hyperactivity

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Background and Purpose Patients with muscle-specific tyrosine kinase (MuSK) antibody (MuSK-Ab)-positive myasthenia gravis (MG) show distinct responses to acetylcholinesterase inhibitors (AChEIs). Although clinical responses to AChEIs in MuSK-Ab MG are reasonably well known, little is known about the electrophysiologic responses to AChEIs. We therefore investigated the clinical and electrophysiologic responses to AChEIs in MuSK-Ab-positive MG patients.

Methods We retrospectively reviewed the medical records and electrodiagnostic findings of 17 MG patients (10 MuSK-Ab-positive and 7 MuSK-Ab-negative patients) who underwent electrodiagnostic testing before and after a neostigmine test (NT).

Results The frequency of intolerance to pyridostigmine bromide (PB) was higher in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (50% vs. 0%, respectively; p=0.044), while the maximum tolerable dose of PB was lower in the former (90 mg/day vs. 480 mg/day, p=0.023). The frequency of positive NT results was significantly lower in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (40% vs. 100%, p=0.035), while the nicotinic side effects of neostigmine were more frequent in the former (80% vs. 14.3%, p=0.015). Repetitive compound muscle action potentials (R-CMAPs) developed more frequently after NT in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (90% vs. 14.3%, p=0.004). The frequency of a high-frequency-stimulation-induced decrement-increment pattern (DIP) was higher in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (100% vs. 17.7%, p=0.003).

Conclusions These results suggest that MuSK-Ab-positive MG patients exhibit unique and hyperactive responses to AChEIs. Furthermore, R-CMAP and DIP development on a standard AChEI dose may be a distinct neurophysiologic feature indicative of MuSK-Ab-positive MG.

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Key Words myasthenia gravis, acetylcholinesterase inhibitor, muscle-specific tyrosine kinase, repetitive compound muscle action potential.

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Introduction

About half of the patients with acetylcholine-receptor-antibody (AChR-Ab)-negative myasthenia gravis (MG) have antibodies against muscle-specific tyrosine kinase (MuSK-Ab). Although MG patients with MuSK-Ab have similar clinical features to patients with AChR-Ab, they show several distinct characteristics such as a predominance of female patients, predominant bulbar and neck weakness, more frequent myasthenic crisis, and a tendency to develop muscle atrophy.[1-4] In addition, MuSK-Ab-positive MG patients exhibit distinct responses to acetyl-

cholinesterase (AChE) inhibitors (AChEIs), including overt worsening of MG symptoms, frequent cholinergic side effects, decreased therapeutic responsiveness to AChEIs, and frequent negative results of diagnostic AChEI tests.[1,2,5] Although it is well known that MuSK-Ab-positive MG patients have distinct clinical responses to AChEIs, little is known about the electrophysiologic responses to AChEIs.

Repetitive compound muscle action potentials (R-CMAPs) were previously demonstrated in a MuSK-Ab-positive MG patient taking the standard dose of AChEI.[6] R-CMAPs represent cholinergic neuromuscular hyperactivity and occur in several conditions, such as congenital AChE deficiency, slow-channel congenital myasthenic syndrome, and organophosphate poisoning.[7] Although R-CMAPs may also be observed in MG patients with AChEI overdose, they are seldom seen in MG patients taking the standard dose.[6] In addition to R-CMAPs, a decrement-increment pattern (DIP) elicited by high-frequency repetitive nerve stimulation may also be observed in conditions with cholinergic neuromuscular hyperactivity, such as organophosphate poisoning.[8]

Based on the observation that MuSK-Ab-positive MG patients exhibit distinct responses to AChEIs, we hypothesized that MuSK-Ab-positive MG patients are more sensitive than MuSK-Ab-negative MG patients to AChEIs. We tested this by investigating the clinical and electrophysiologic characteristics of MuSK-Ab-positive MG patients who underwent an electrodiagnostic testing (EDx) before and after a diagnostic neostigmine test (NT).

Methods

We retrospectively reviewed the medical records of MG patients who underwent EDx and NT from 2007 to 2010 at Severance Hospital, Yonsei University Health System. The evaluation of MG patients in our electrodiagnostic laboratory usually involves a clinical evaluation, EDx, and NT. To confirm the presence of objective electrophysiologic responsiveness to AChEIs, EDx may be repeated 30−45 minutes after neostigmine injection at the examiner's discretion. We selected 17 MG patients who underwent anti-AChR and anti-MuSK antibody tests and EDx before and after NT. All of the 17 patients underwent EDx and NT at the initial diagnosis stage. MG was diagnosed based on the symptoms and signs of muscle fatigue, decrement responses on low-frequency repetitive nerve stimulation (RNS), serum levels of AChR and MuSK antibodies, and improvement of muscle fatigue after the intramuscular injection of neostigmine. Antibody analyses were performed using commercially available assays (anti-AChR-binding antibody, Seoul Clinical Laboratories, Seoul, Korea; anti-MuSK antibody, Athena Diagnostics, Worcester, MA, USA). The test for anti-AChR-binding antibody was considered to be negative if the value was ≤0.2 nmol/L. The results of the anti-MuSK antibodies test were categorized into negative (<10 titer units), borderline (≥10 titer units and <20 titer units), or positive (≥20 titer units).

In all 17 patients, EDx included baseline RNS and post-NT ulnar nerve stimulation recordings on the abductor digiti minimi (ADM). The RNS was performed according to previously described methods on the ADM and flexor carpi ulnaris (FCU) muscles with ulnar nerve stimulation at the elbow, on the orbicular oculi and nasalis muscles with facial nerve stimulation, and on the trapezius muscle with spinal accessory nerve stimulation using the Neuroscreen system (Toennies, Bavaria, Germany) or the Schwarzer topas EMG system (Natus, Bavaria, Germany).[9,10] A compound muscle action potential (CMAP) decrement of ≥10% was considered abnormal. In patients taking pyridostigmine bromide (PB), the EDx was performed at least 12 hours after the last dose. NT was performed after baseline clinical examination and EDx. The response was evaluated at about 30 minutes after the intramuscular injection of neostigmine methylsulfate (0.02 mg/kg). Atropine (1 mg) was administered several minutes before the neostigmine injection. The side effects of neostigmine were described. Nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, and diaphoresis were regarded as muscarinic side effects, and muscle cramps, fasciculation, weakness, and a tightness sensation on any part of the body were regarded as nicotinic effects.

The results of EDx were reviewed by two neurologists (H.J.P. and H.E.L.) who were blinded to clinical information. The two neurologists consensually determined the presence of R-CMAP and a DIP on the ADM muscle at normal gain (5 mV/division). R-CMAP was defined as a CMAP followed by repetitive discharges that did not exist prior to NT (Fig. 1). A DIP was defined as the pattern of RNS that shows the maximum decrement of amplitude in the second CMAP and then progressive recovery of the amplitude from the third CMAP (Fig. 2).

We obtained patients' background information from their medical records, including the age at MG symptom onset, symptoms at disease onset, sex, Myasthenia Gravis Foundation of America (MGFA) clinical classification, results of anti-AChR-binding and anti-MuSK antibody tests, follow-up duration, MGFA postintervention status, maximum tolerable dose of PB, maintenance dose of PB, and intolerance to PB. Intolerance to PB was defined as being unable to take PB due to cholinergic side effects such as severe muscle fasciculations, abdominal cramps, hypersalivation, or blurred vision. Age and disease duration at EDx, RNS results, MG activities of daily living (MG-ADL) score, baseline quantitative MG (QMG) score, NT results, and side effects of neostigmine were ob-

tained from EDx reports.

The requirement for obtaining informed consent from the study subjects was waived by the institutional review board of Severance Hospital.

Statistical analysis

The Mann-Whitney U test and Fisher's exact test were used to compare continuous and categorical variables, respectively. All statistical analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). A two-tailed probability value of $p<0.05$ was considered statistically significant.

Results

The clinical characteristics of the subjects are summarized in Table 1. There were ten MuSK-Ab-positive and seven MuSK-Ab-negative MG patients. Three MuSK-Ab-positive patients (prednisolone 10 mg/day; prednisolone 50 mg/day; azathioprine 50 mg/day) and two MuSK-Ab-negative MG patients (prednisolone 45 mg/day; cyclosporine 200 mg/day) were treated with immune-modifying therapy. All MuSK-Ab-positive MG patients were negative for anti-AChR-binding antibody. Four of the seven MuSK-Ab-negative MG patients were positive for anti-AChR-binding antibody. The age at disease onset, symptoms at disease onset, follow-up duration, and maintenance dose of PB did not differ significantly between MuSK-Ab-positive and MuSK-Ab-negative patients. The frequency of intolerance to PB was higher in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (50% vs. 0%, respectively; $p=0.044$), while the maximum tolerable dose of PB was lower in the former (90 mg/day vs. 480 mg/day, $p=0.023$).

The results of EDx and NT are summarized in Table 2. The age at EDx, disease duration, MG-ADL score, and QMG

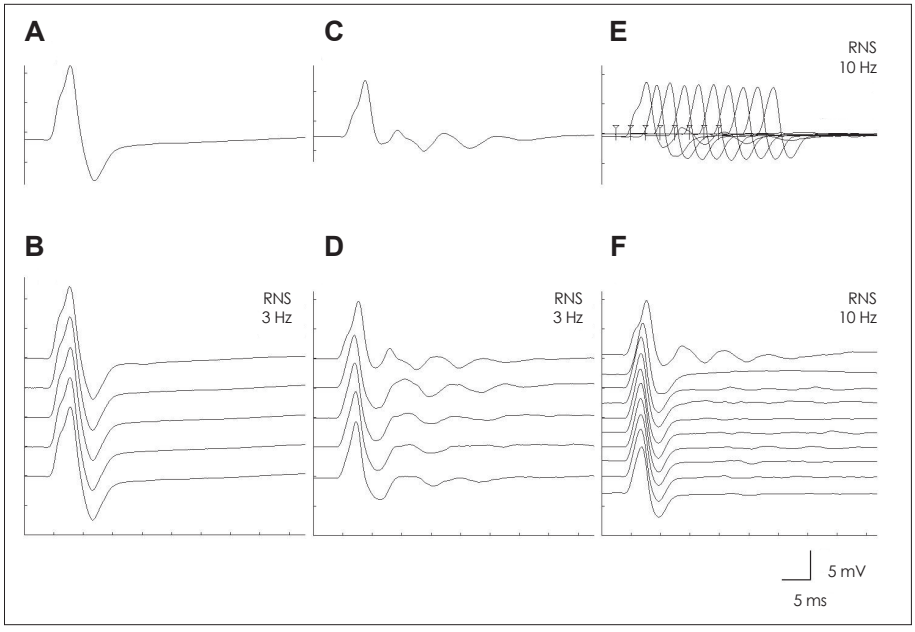

Fig. 1. Recording from the abductor digiti minimi muscle. Data are from a single muscle-specific tyrosine kinase antibody-positive myasthenia gravis patient. Repetitive discharges were not seen in the baseline electrodiagnostic testing (A and B) after the first compound muscle action potential (CMAP). Repetitive CMAPs were demonstrated after the intramuscular injection of neostigmine methylsulfate (0.02 mg/kg) (C–F). On repetitive nerve stimulation (RNS) at 3 Hz, the repetitive discharges after the first CMAP were diminished by the second stimulation (D). This reduction was more definite for 10-Hz RNS (E and F).

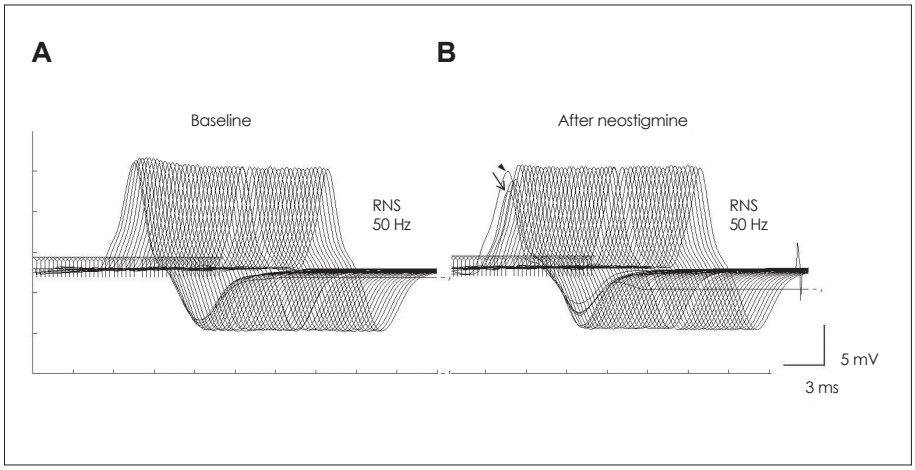

Fig. 2. Recording from the abductor digiti minimi muscle for high-frequency repetitive nerve stimulation at 50 Hz for 1 second before (A) and after (B) neostigmine injection. Data are from a single muscle-specific tyrosine kinase-antibody-positive myasthenia gravis patient. After the intramuscular injection of neostigmine methylsulfate (0.02 mg/kg), 50-Hz RNS showed a decrement-increment pattern that was not demonstrated before neostigmine injection. After neostigmine injection, 50-Hz RNS resulted in the amplitude of the second compound mascle action potential (CMAP) (arrow) being reduced maximally compared to the first CMAP (arrowhead), while the amplitude progressively recovered from the third CMAP (B).

Table 1. Clinical characteristics of MG patients with and without MuSK-Ab

Characteristic	MuSK- (*n*=7)	MuSK+ (*n*=10)	*p**
Onset age, median (range), years	44.0 (23–48)	37.0 (20–52)	0.353
Female, *n* (%)	3 (42.9)	10 (100)	0.015
AChR-Ab seropositivity, *n* (%)	4 (57.1)	0 (0)	0.015
Onset symptoms			
Ocular, *n* (%)	4 (57.1)	8 (80.0)	0.314
Bulbofacial, *n* (%)	3 (42.9)	2 (20.0)	
F/U duration, median (range), months	33.0 (22–46)	41.0 (33–70)	0.063
MGFA clinical classification			
IIa, *n*	2	0	
IIb, *n*	2	2	
IIIb, *n*	1	4	
IVb, *n*	1	3	
V, *n*	1	1	
MGFA postintervention status at last visit			
PR, *n*	4	3	
MM-1, *n*	0	6	
MM-2, *n*	0	1	
MM-3, *n*	2	0	
Worse, *n*	1	0	
Intolerance to PB, *n* (%)	0 (0)	5 (50.0)	0.044
Maximum tolerable dose of PB, median (range), mg	480 (120–600)	90 (0–480)	0.023
Maintenance dose of PB, median (range), mg	0 (0–240)	0 (0–120)	0.100

*p values were determined using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.
AChR-Ab: acetylcholine receptor antibody, F/U: follow up, MG: myasthenia gravis, MGFA: Myasthenia Gravis Foundation of America, MM: minimal manifestation, MuSK-Ab: muscle-specific tyrosine kinase antibody, MuSK-: MuSK-antibody negative, MuSK+: MuSK-antibody positive, PB: pyridostigmine bromide, PR: pharmacologic remission.

score did not differ significantly between MuSK-Ab-positive and MuSK-Ab-negative patients. Five MuSK-Ab-negative patients (71.4%) exhibited abnormal decrement responses during baseline RNS in the ADM and FCU, whereas none of the MuSK-Ab-positive patients (0%) exhibited abnormal responses (p=0.003). Positive NT results were significantly less frequent in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (40% vs. 100%, p=0.035). The nicotinic side effects of neostigmine were more frequent in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (80% vs. 14.3%, p=0.015). After neostigmine injection, R-CMAPs in the ADM developed more frequently in MuSK-Ab-positive patients than in MuSK-Ab-negative patients (90% vs. 14.3%, p=0.004). High-frequency stimulation of the ulnar nerve (50 Hz for 1 second) was performed after neostigmine injection in eight MuSK-Ab-positive and six MuSK-Ab-negative patients; the frequency of a DIP was higher in the MuSK-Ab-positive patients than in MuSK-Ab negative patients (100% vs. 17.7%, p=0.003). R-CMAP was demonstrated in all patients with a DIP.

Discussion

The MuSK-Ab-positive MG patients in the present study showed several features suggestive of cholinergic neuromuscular hyperactivity to AChEIs. Intolerance to PB and nicotinic side effects to neostigmine were more frequent in MuSK-Ab-positive MG patients than in MuSK-Ab-negative patients. The maximum tolerable dose of PB was lower in MuSK-Ab-positive patients, and negative NT results were more frequent in MuSK-Ab-positive patients. These findings are consistent with those of previous studies.[1,2,5] In addition, the present study has provided electrophysiologic evidence of cholinergic neuromuscular hyperactivity in MuSK-Ab-positive MG patients, in whom the frequencies of R-CMAPs and a DIP on the standard diagnostic dose of neostigmine were significantly higher than in MuSK-Ab-negative patients.

R-CMAP is a well-known electrophysiologic feature of congenital AChE deficiency, in which deficiency of neuromuscular-junction (NMJ) AChE prolongs the exposure of AChR to acetylcholine, resulting in prolonged endplate potentials whose amplitude remains above threshold for longer than the absolute refractory period of the muscle fiber.[11] A DIP is a characteristic electrophysiologic feature of acute poisoning by

Table 2. Results of electrodiagnostic and neostigmine testing of MG patients with and without MuSK-Ab

	MuSK- (*n*=7)	MuSK+ (*n*=10)	*p**
Age at examination, median (range), years	44.0 (26–48)	42.0 (20–57)	0.768
Disease duration, median (range), months	3.0 (1–89)	16.5 (3–302)	0.078
MG-ADL score, median (range)	6.0 (3–14)	9.0 (4–18)	0.170
Baseline QMG score, median (range)	8.0 (4–19)	13.0 (8–26)	0.056
CMAP decrement on RNS of ≥10%			
ADM, *n* (%)	5 (71.4)	0 (0)	0.003
FCU, *n* (%)	5 (71.4)	0 (0)	0.003
OO, *n* (%)	5 (71.4)	8 (80.0)	1.000
Nasalis, *n* (%)	5 (71.4)	10 (100)	0.154
Trapezius, *n* (%)	5 (71.4)	5 (50.0)	0.622
Neostigmine test			
Positivity, *n* (%)	7 (100)	4 (40.0)	0.035
Side effects of neostigmine			
Muscarinic only, *n* (%)	5 (71.4)	1 (10.0)	
Nicotinic only, *n* (%)	0 (0)	1 (10.0)	
Muscarinic and nicotinic, *n* (%)	1 (14.3)	7 (70.0)	
No side effects, *n* (%)	1 (14.3)	1 (10.0)	
R-CMAP, *n* (%)	1 (14.3)	9 (90.0)	0.004
Ulnar-nerve RNS at 50 Hz for 1 second, *n*	6	8	
DIP, *n* (%)	1 (17.7)	8 (100)	0.003

*p values were determined using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.
ADM: abductor digiti minimi, CMAP: compound muscle action potential, DIP: decrement-increment pattern, FCU: flexor carpi ulnaris, MG-ADL: myasthenia gravis activities of daily living, MuSK-Ab: muscle-specific tyrosine kinase antibody, MuSK-: MuSK-antibody negative, MuSK+: MuSK-antibody positive, OO: orbicularis oculi, QMG: quantitative myasthenia gravis, R-CMAP: repetitive CMAP, RNS: repetitive nerve stimulation.

organophosphate, which induces irreversible AChE inhibition and causes an AChE-deficient status in the NMJ.[8] Although the pathomechanism of a DIP is poorly understood, stimulus-induced antidromic backfiring and maximal end-plate depolarization after the first stimulation may play important roles in the generation of a DIP.[8] Thus, an AChE-deficient status is associated with the generation of R-CMAPs and a DIP. At the NMJ, AChE is linked to collagen Q (ColQ), which binds to perlecan and MuSK. The ternary complex consisting of ColQ, perlecan, and MuSK is important for the synaptic localization of AChE at the NMJ. Previous studies did not detect clustering of AChE in MuSK-deficient myotubes, and found that the passive transfer of anti-MuSK antibodies reduced the size and density of ColQ at the NMJ of mice.[12,13] Based on these results, the NMJs of MuSK-Ab-positive MG patients are predicted to be deficient in synaptic AChE, which leads to overreaction to AChEIs and the generation of R-CMAPs and a DIP. In a recent experiment the administration of therapeutic doses of neostigmine evoked R-CMAPs in 94% of MuSK-Ab-positive MG mice but in only 22% of MuSK-Ab-negative MG mice.[14] Accordingly, our data suggest that R-CMAPs and/or a DIP elicited by the standard dose of AChEI represent an AChE-deficient status at the NMJ in MuSK-Ab-positive MG patients.

One of the MuSK-Ab-negative patients in this study showed both R-CMAPs and a DIP. This patient was a 26-year-old woman who had mild ptosis, diplopia, and dysarthria with fluctuation (MGFA clinical classification IIb), and was negative for anti-AChR-binding antibodies. Her ptosis and diplopia definitely improved after neostigmine injection, but this also resulted in side effects of a tightness sensation on the neck, fasciculation, and abdominal cramps. Although the assay for MuSK antibodies was negative, there was clinical suspicion of MuSK-Ab-positive MG. The possibility of a false-negative anti-MuSK antibody result was therefore considered in this patient.

Because neostigmine methylsulfate acts for longer than edrophonium chloride, both clinical and electrophysiological responses could be evaluated. However, patients could suffer from side effects for longer if these develop after neostigmine injection. A standard dose of neostigmine methylsulfate (0.02 mg/kg) was used to diagnose MG in this study. Although 1 mg of atropine was administered several minutes beforehand to reduce muscarinic effects, 15 of 17 subjects (88%) exhibited adverse responses to neostigmine. The most common muscarinic side effects were abdominal cramps and increased peristalsis, and the most common nicotinic side effects were fasciculation and a sensation of neck tightness. The neostigmine

side effects were mild in almost all of the patients, and subsided within 1 hour without treatment. However, one MuSK-Ab-positive patient showed severe fasciculation over the entire body along with diaphoresis and increased salivation, which lasted for 1.5 hours (the patient was observed closely until the side effects subsided). This indicates the need to observe patients closely for at least 1 hour after neostigmine injection.

This study was subject to several limitations. First, the retrospective design of the study and the small sample might mean that the conclusions are not generalizable. The main reason for the small sample in this study is that anti-MuSK antibody assay was applied to few of the MG patients due to the inconvenience of this assay. Anti-MuSK antibody analysis was performed in the generalized MG patients who had predominant bulbar symptoms and/or seronegativity for anti-AChR-binding antibody. There is a possibility of selection bias whereby the MuSK-Ab-negative group may have included clinically suspected MuSK-Ab-positive patients with false-negative MuSK-Ab assay results. Second, there was another selection bias problem, in that the EDx after NT was applied only to a small proportion of the MG patients at the examiner's discretion. Third, since we observed R-CMAPs using a surface recording electrode at normal gain, we could not apply a previously used grading system.[15] Furthermore, we may have missed R-CMAPs whose repetitive discharges had very low amplitudes following the first CMAP. Even so, all patients with R-CMAPs definitely exhibited repetitive discharges, whereas none of the patients with no R-CMAP were suspected of exhibiting repetitive discharges. Together these limitations mean that studies with larger samples and well-designed EDx for detecting and grading R-CMAPs are necessary to validate the hypothesis that MuSK-Ab-positive MG patients are more sensitive than MuSK-Ab-negative patients to AChEIs.

In conclusion, MuSK-Ab-positive MG patients exhibit distinct responses to AChEIs, including intolerance to AChEIs, frequent nicotinic side effects, and frequent negative results for diagnostic AChEI tests. Furthermore, R-CMAP and DIP development on a standard AChEI dose are associated with MuSK-Ab-positive MG. These features suggest the presence of cholinergic neuromuscular hyperactivity in MuSK-Ab-positive MG and may be helpful for the diagnosis of MuSK-Ab-positive MG.

Conflicts of Interest

The authors have no financial conflicts of interest.

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