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# Clinical significance of repetitive compound muscle action potential in myasthenia gravis patients



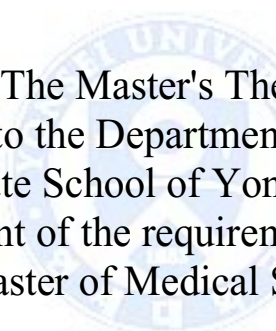
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# Clinical significance of repetitive compound muscle action potential in myasthenia gravis patients

Directed by Professor Seung Min Kim



The Master's Thesis  
submitted to the Department of Medicine,  
the Graduate School of Yonsei University  
in partial fulfillment of the requirements for the degree of  
Master of Medical Science

Hyo Eun Lee

June 2015

This certifies that the Master's Thesis of  
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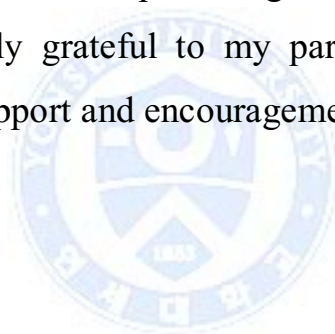
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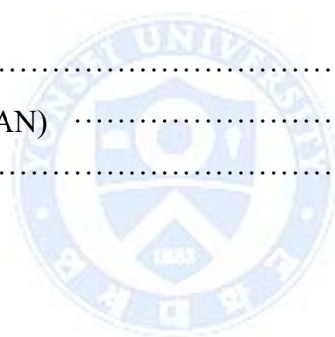
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## ABSTRACT

### Clinical significance of repetitive compound muscle action potential in myasthenia gravis patients

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Repetitive compound muscle action potentials (R-CMAPs) are multiple compound muscle action potentials (CMAPs) following an initial CMAP induced by a single stimulation of a nerve. R-CMAPs indicate cholinergic neuromuscular hyperactivity, and occur in several conditions, such as congenital acetylcholinesterase (AChE) deficiency, slow-channel congenital myasthenic syndrome, and organophosphate poisoning. Although R-CMAPs may also be observed in myasthenia gravis (MG) patients with AChE inhibitor overdose, these are seldom seen in MG patients with the standard dose. The mechanism of R-CMAP induction and its clinical significance in patients with MG is also unclear. Therefore, we investigated the clinical characteristics of MG patients with R-CMAPs who were given the standard diagnostic dose of neostigmine. We retrospectively reviewed the medical records and electrodiagnostic findings of patients who underwent electrodiagnostic tests before and after the neostigmine test. Of the 71 MG patients reviewed, 24 developed R-CMAPs after receiving the standard diagnostic dose of neostigmine. There were no significant differences in age at disease onset, myasthenia gravis activities of daily living score, disease



duration, and follow-up duration. Decremental response on the baselinerepetitive nerve stimulation (RNS) test was lower in the R-CMAP group. This group had a higher frequency of side effects and intolerance to, and a lower maximal tolerable dose of pyridostigmine bromide (PB). The appearance of R-CMAPs after a standard dose of injected neostigmine may be a good indicator of the risk of PB side effects. The detection of R-CMAPs after neostigmine injection may help in creating a therapeutic plan for myasthenia gravis patients.



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Key words : myasthenia gravis, repetitive compound muscle action potential, pyridostigmine bromide

# Clinical significance of repetitive compound muscle action potential in myasthenia gravis patients

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## I. INTRODUCTION

Myasthenia gravis (MG), an autoimmune disorder affecting neuromuscular transmission, is characterized by weakness of voluntary muscles and fatigue. The identification of impaired neuromuscular transmission is an essential step for the diagnosis of MG. Therefore, electrodiagnostic studies including repetitive nerve stimulation (RNS) and single-fiber electromyography are used to evaluate the electrophysiological status of the neuromuscular junction.<sup>1,2</sup>

Repetitive compound muscle action potentials (R-CMAPs) are multiple compound muscle action potentials (CMAPs) observed after an initial CMAP by a single stimulation of a nerve. The mechanism of R-CMAP production remains unclear. A generally accepted mechanism of R-CMAP is described below. The stimulation of presynaptic acetylcholine (ACh) receptors can lead to backfiring of nerve action potentials.<sup>3,4</sup> Excess ACh prolongs the activation of the postsynaptic receptor, resulting in prolonged open channel time and end-plate potentials.<sup>2,3,5</sup> These abnormal synaptic events reactivate the nerve fiber, leading to re-excitation of the muscle fiber of the motor unit.<sup>5</sup> A single nerve stimulation may elicit not only a single CMAP, but also multiple R-CMAPs following the initial CMAP in some neuromuscular junction disorders, such as organophosphate intoxication, congenital acetylcholinesterase deficiency, and

slow-channel congenital myasthenic syndrome.<sup>5-9</sup> These R-CMAPs result from the repetitive discharge of muscle fibers after a single stimulation, and represent the electrophysiological status of cholinergic neuromuscular hyperactivity.<sup>8</sup>

In patients with MG, R-CMAPs may be caused by acetylcholinesterase (AChE) inhibitor overdose.<sup>7</sup> However, R-CMAPs are rarely seen in patients with MG taking a standard dose of AChE inhibitors.<sup>8,10</sup> In a previous study, MG patients with nicotinic side effects of AChE inhibitors developed R-CMAP more frequently than patients without the side effects.<sup>7</sup> In addition, R-CMAPs have been frequently observed in muscle-specific tyrosine kinase (MuSK) antibody-positive MG patients during a diagnostic neostigmine test. A substantial number of MuSK antibody-positive MG patients with R-CMAPs cannot tolerate AChE inhibitors due to their cholinergic side effects.<sup>8</sup> These findings suggest that R-CMAPs may predict the risk of side effects and intolerance to oral AChE inhibitors by representing the cholinergic activity status at the neuromuscular junction. Despite the two aforementioned studies, little is known about the clinical significance of R-CMAP in patients with myasthenia gravis.

Therefore, we investigated the clinical characteristics of myasthenia gravis patients with R-CMAP in order to identify its clinical usefulness in therapeutic decision-making.

## II. MATERIALS AND METHODS

We retrospectively reviewed the clinical records and eletrodiagnostic findings of MG patients who underwent electrodiagnostic studies (EDx) and diagnostic neostigmine tests (NT) from 2007 to 2015 at Severance Hospital. The diagnosis of MG was based on the symptoms and signs of muscle fatigue, decrement responses on low rate RNS, serum level of anti-AChR and MuSK antibodies, and the improvement of muscle fatigue after the intramuscular injection of neostigmine. Antibody analyses were performed through 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 negative if the value was  $\leq 0.2$  nmol/L. The result of anti-MuSK antibodies tests were expressed as negative ( $<10$ ), borderline ( $\geq 10$ ,  $<20$ ), or positive ( $\geq 20$ ). When patients with MG are evaluated in our electrodiagnostic laboratory, they usually undergo clinical evaluation, EDx, and NT. To confirm objective electrophysiology responsiveness to neostigmine methylsulfate, EDx may be repeated 30-45 minutes after neostigmine injection at the examiner's discretion.

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, flexor carpi ulnaris (FCU) muscles with the ulnar nerve stimulation at the elbow, the orbicular oculi (OO), nasalis muscles with the facial nerve stimulation, and the trapezius muscle with spinal accessory nerve stimulation using the Neuroscreen system (Toennies, Bavaria, Germany) or the Schwarzer topas EMG system (Natus, Bavaria, Germany)<sup>8</sup>. A decrement of CMAP  $\geq 10\%$  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 approximately 30 minutes after intramuscular injection

of 0.02 mg/kg neostigmine methylsulfate. The side effects of neostigmine were recorded.

A total of 79 patients with MG underwent EDx before and after NT. Exclusion criteria were as follows: overdose of neostigmine methylsulfate, incomplete medical records, or less than twelve months of follow up. The patients were classified into two groups according to the development of R-CMAP after NT. R-CMAP was defined as a CMAP followed by repetitive discharges that did not exist before NT (Fig. 1).

Two neurologists (L.H.S and P.B.S) without clinical information about the patients reviewed the results of EDx. The two neurologists consensually determined the presence of R-CMAP on the ADM muscle at normal gain (5 mV/division).

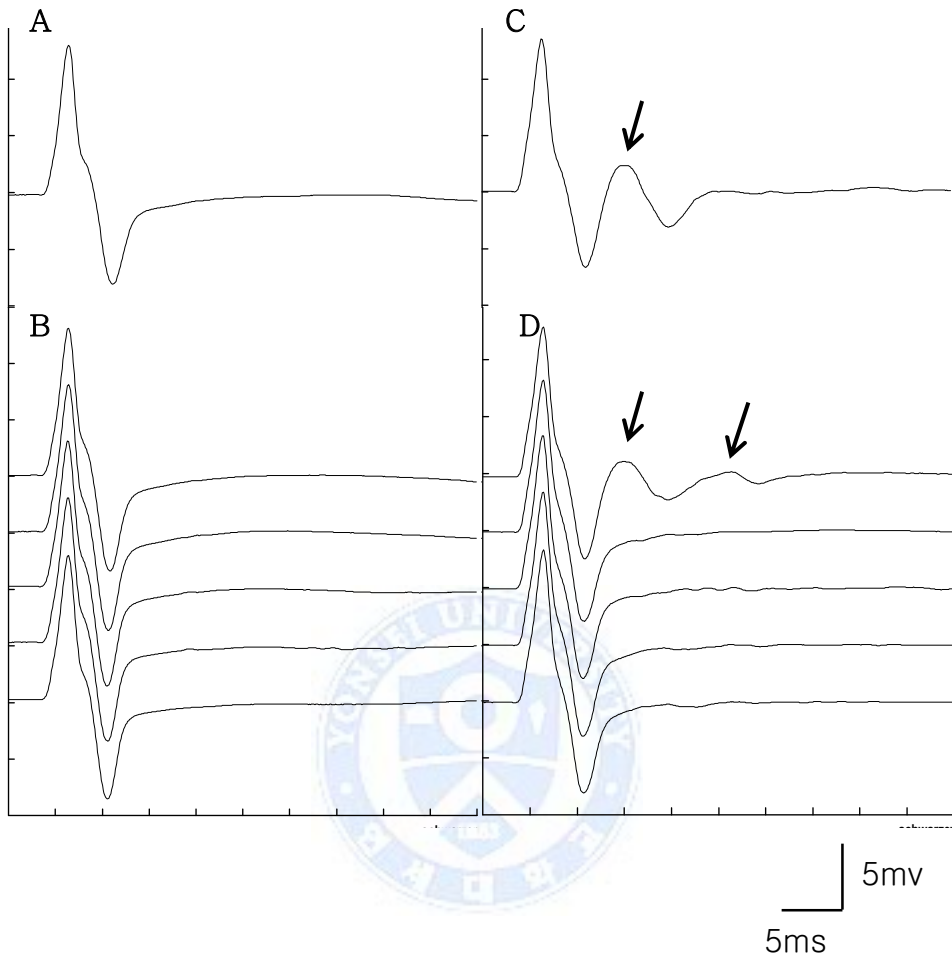
We obtained patients' background information from their medical records, including age of MG symptom onset, sex, myasthenia gravis foundation of America (MGFA) clinical classification at the first visit, the worst MGFA clinical classification during follow up, results of anti-AChR-binding and anti-MuSK antibody tests, thymoma, follow-up duration, MGFA postintervention status, maximal tolerable dose of PB, and intolerance to PB. Intolerance to PB was defined as an inability to take PB due to cholinergic side effects such as severe muscle fasciculation, abdominal cramps, hypersalivation, and blurred vision. Age at EDx, disease duration, RNS results, myasthenia gravis activities of daily living (MG-ADL) score, baseline quantitative myasthenia gravis (QMG) score, result of NT, and side effects of neostigmine were obtained from EDx reports.

This study was approved by the institutional review board of Severance Hospital, Yonsei University Health System, and the requirement for informed consent from the study subjects was waived.

**Statistical analysis**

All data are expressed as the median (interquartile range) for skewed continuous variables. Comparisons of continuous variables for the two groups were performed using the Mann-Whitney U test. The Chi-square test (Pearson's and Fisher's exact test) was used for the comparison of the categorical variables between groups. All statistical analyses were performed using the IBM SPSS Statistics software for Windows Version 21.0 (IBM Corp., Armonk, NY, USA). A two-tailed probability value of  $p < 0.05$  was considered statistically significant.





**Figure 1.** RNS test on ADM stimulation by ulnar nerve at the elbow. (A) R-CMAP was not showed on single stimulation of nerve. (B) There was no decremental response by low frequency (3Hz) RNS test. (C, D) R-CMAP (arrow) was presented following initial CMAP after 30min of neostigmine methylsulfate injection.

### III. RESULTS

Among the 79 patients who underwent EDx before and after NT, 71 patients were included in this study and eight were excluded. Seven patients had less than twelve months of follow up. One patient had incomplete medical records. None of these patients had R-CMAPs on baseline RNS tests.

#### 1. Clinical manifestations

The clinical characteristics of the patients are summarized in Table 1. There were no significant differences in age at disease onset (39.5 vs. 34.0 years,  $p = 0.189$ ), thymoma (16.7 vs. 19.1%,  $p = 1.000$ ), and follow-up duration (36.5 vs. 34.0 months,  $p = 0.742$ ) between the R-CMAP group and the no-R-CMAP group. The R-CMAP group showed ocular type (41.7 vs 14.9%,  $p = 0.012$ ) and female (91.7 vs. 57.4%,  $p = 0.003$ ) predominance. The Ach receptor antibody (Ab) seropositivity was lower in the R-CMAP group than in the no R-CMAP group (58.3 vs. 85.1%,  $p = 0.012$ ). Although we did not perform MuSK-Ab detection for all patients, anti-Musk antibodies were found in 17 patients. Nine patients revealed MG with MuSK-Ab. Of these, eight patients were in the R-CMAP group (90 vs. 10%,  $p = 0.015$ ), and one patient was in the no R-CMAP group. The antibody status of the subgroup of patients in which MuSK-Abs were checked is summarized in Table 2.

#### 2. Repetitive nerve stimulation (RNS) test and neostigmine test (NT)

There were no significant differences in age at exam (44 vs. 39 years,  $p = 0.069$ ), MG-ADL score at the RNS test (5.5 vs. 7.0,  $p = 0.390$ ), and disease duration (60.0 vs. 63.0 months,  $p = 0.456$ ) between the R-CMAP group and the no-R-CMAP group. The decremental response on the baseline RNS test was



lower in the R-CMAP group (62.5 vs. 91.5%,  $p = 0.007$ ) (Table 3). After 30 minutes of neostigmine methylsulfate injection, R-CMAPs were found in the 24 patients after repeated ulnar nerve stimulation recording on the ADM (Fig. 1).

The R-CMAP group had fewer positive results in the neostigmine test, and lower differences between baseline QMG scores and post-neostigmine QMG scores. All patients in the R-CMAP group had neostigmine-related side effects (100 vs. 70.2%,  $p = 0.002$ ). Twenty-three patients in the R-CMAP group had neostigmine-related muscarinic side effects; 23 patients had abdominal pain, one developed diarrhea. Thirty-two patients in the no-R-CMAP group had neostigmine-related muscarinic side effects: 29 had abdominal pain, five complained of diarrhea, one had nausea, and three had increased salivation. Nicotinic side effects of neostigmine were especially more frequent in the R-CMAP group (75.0 vs. 6.4%,  $p < 0.001$ ). Eighteen patients in the R-CMAP group had nicotinic side effects; 17 had muscle fasciculation and two had squeezing sensation in the neck. Only three patients of the no R-CMAP group had nicotinic side effects: three had muscle fasciculation, and one had squeezing sensation in the neck.

### **3. Side effects of pyridostigmine bromide (PB)**

PB is one of the most commonly used AChE inhibitors for the treatment of myasthenia gravis in patients included in this study. Table 4 shows the side effects of PB. The R-CMAP group had a lower maximal tolerable dose of PB (240 vs. 480 mg/day,  $p < 0.001$ ) and a higher frequency of PB intolerance (37.5 vs. 0%,  $p < 0.001$ ). Nine patients in the R-CMAP group had intolerance to PB. The most commonly given reasons for intolerance were abdominal pain and muscle fasciculation. In the no-R-CMAP group, six patients showed discomfort about taking PB; complaints resolved after decreasing the dose of PB. The other patients in the no-R-CMAP group tolerated PB well. Side effects of PB were

more frequent in the R-CMAP group (45.8 vs. 12.8%,  $p < 0.001$ ). Nicotinic side effects of PB were especially more frequent in the R-CMAP group (20.8 vs. 4.3%,  $p = 0.040$ ).



**Table 1.** Clinical characteristics of myasthenia gravis patients with and without R-CMAP

	R-CMAP (n=24)	no R-CMAP (n=47)	p- value
Onset age, median (IQR), years	39.5 (28.0–50.8)	34.0 (28.0–44.0)	0.189
Female, n (%)	22 (91.7)	27 (57.4)	0.003
Follow up duration, month, median (IQR)	57.5 (49.5–64.0)	56.0 (47.0–63.0)	0.316
AChR Ab seropostivity, n (%)	14 (58.3)	40 (85.1)	0.012
AChR Ab titier , median (IQR), nmol/L	1.23 (0.01–7.62)	8.15 (0.63–11.62)	0.011
Thymoma, n (%)	4 (16.7)	9 (19.1)	1.000
MGFA clinical classification at first visit			
I, n	10	7	0.012*
IIa, n	1	19	
IIb, n	10	3	
IIIa, n	1	9	
IIIb, n	1	7	
IVa, n	0	1	
IVb, n	1	1	
MGFA worst			
I, n	4	7	
IIa, n	6	11	
IIb, n	6	1	
IIIa, n	2	14	
IIIb, n	1	2	
IVa, n	1	3	
IVb, n	3	4	
V, n	1	5	

\* p-value; I vs. other MGFA

CMAP, compound muscle action potential; IQR, interquartile range; MG, myasthenia gravis; AChR Ab, acetylcholine receptor antibody; MGFA, Myasthenia Gravis Foundation of America

**Table 2.** Antibody status in subgroup patients who checked MuSK Ab

	R-CMAP (N=10)	no R-CMAP (N=7)
MuSK Ab positivity, n	8	1
MuSK Ab positivity, only, n	6	0
Double seropositive, n	2	1

CMAP, compound muscle action potential; MuSK Ab, muscle specific tyrosine kinase antibody



**Table 3.** Result of low frequency repetitive nerve stimulation test and neostigmine test

	R-CMAP (N=24)	no R-CMAP (N=47)	p- value
Age at examination, median (IQR), years	44.0 (32.0–55.8)	39.0 (29.0–47.0)	0.069
Disease duration, median (IQR), months	60.0 (54.5–76.3)	63.0 (52.0–107.0)	0.456
MG ADL score at RNST, median (IQR)	5.5 (3.3–8.8)	7.0 (3.0–10.0)	0.390
CMAP decremental on baseline RNST of $\geq 10\%$ , n (%)	15 (62.5)	43 (91.5)	0.007
ADM, n (%)	0 (0.0)	29 (61.7)	<0.001
FCU, n (%)	4 (16.7)	34 (72.3)	<0.001
OO, n (%)	12 (50.0)	35 (74.5)	0.039
Nasalis, n (%)	12 (50.0)	41 (87.2)	0.001
Trapezius, n (%)	8 (33.3)	32 (68.1)	0.005
Result of neostigmine test			
Positivity of neostigmine test, n (%)	16 (66.7)	44 (93.6)	0.005
Baseline QMG score, median (range)	8.5 (7.3–13.3)	13.0 (8.0–18.0)	0.046
Change in QMG score, median (range)	3 (2.0–4.8)	6 (2.0–9.0)	0.017
Side effect of neostigmine, n (%)	24 (100.0)	33 (70.2)	0.002
Nicotinic side effect, n (%)	18 (75.0)	3 (6.4)	<0.001
Muscarinic side effect, n (%)	23 (95.8)	32 (68.1)	0.008

CMAP, compound muscle action potential; IQR, interquartile range; MG-ADL, myasthenia gravis activities of daily living; RNST, repetitive nerve stimulation test; ADM, abductor digiti minimi; FCU, flexor carpi ulnaris; OO, orbicularis oculi; QMG, quantitative myasthenia gravis

**Table 4.** Response to oral pyridostigmine bromide

	R-CMAP (N=24)	no R- CMAP (N=47)	p- value
Maximum tolerable dose of PB, mg/day, median (IQR)	240 (45-480)	480 (480-480)	<0.001
Intolerance to PB, n (%)	9 (37.5)	0 (0.0)	<0.001
Side effect of PB, n (%)	11 (45.8)	6 (12.8)	0.002
Nicotinic side effect, n (%)	5 (20.8)	2 (4.3)	0.040
Muscle cramp	2	1	
Fasciculation	3	1	
Muscarinic side effect, n (%)	6 (25.0)	4 (8.5)	0.077
Diarrhea	0	1	
Abdominal pain	6	4	
Diaphoresis	1	0	
No description, n (%)	1 (4.2)	0 (0.0)	0.338

CMAP, compound muscle action potential; IQR, interquartile range; PB, pyridostigmine bromide

#### IV. DISCUSSION

AChE inhibitors facilitate neuromuscular transmission by inhibiting acetylcholine breakdown at the neuromuscular junction.<sup>11</sup> These drugs are the first-line treatment for MG, and provide temporary relief of the symptoms.<sup>11-13</sup> They are effective as an initial therapy in most patients with MG and may be used as the sole therapeutic agent for long periods in mild forms of MG.<sup>14</sup> Although AChE inhibitors are usually well tolerated at standard doses (for example, up to 60 mg of pyridostigmine bromide five times per day), some patients with MG show cholinergic hypersensitivity and are intolerant of even small doses of AChE inhibitors. In our study, nine patients with MG were intolerant to PB. All of them had R-CMAPs after NT. Despite these side effects, doctors prescribed PB, because it is usually well tolerated and the first-line treatment for MG.<sup>2</sup> Patients eventually discontinued PB and began immunosuppressant therapies. Fortunately, they do not continue to experience the side effects of PB, and their MG symptoms are well controlled. The patients achieved MGFA postintervention status PR or MM at last visit. Therefore, therapeutic management with AChE inhibitors should be individualized. We suggest that R-CMAP after NT is a helpful tool to predict the side effects of PB.

Predicting the distinct responses to AChE inhibitors is very important to prevent unnecessary side effects of AChE inhibitors in MG patients. There are no well-controlled studies to predict the side effects of PB.<sup>15</sup> One method to achieve this is by measuring AChE activities to predict side effects of PB. Various methods are known to determine cholinesterase activities.<sup>16</sup> Ellman's assay is widely used to measure AChE activity but has technical-related limitations.<sup>16,17</sup> In some studies, AChE activities do not correlate with the severity of PB side effects.<sup>18-20</sup> In other studies, only older age correlated with the side effects of an AChE inhibitor.<sup>7</sup> Some studies have established that some patients who present hypersensitivity to AChE inhibitors have a mutation in the

*AChE* gene.<sup>15,21-23</sup> AChE activity measurement and genetic analysis are not commonly used in the clinic. However, it is very easy to test for R-CMAP after NT in a clinical setting. Moreover, it requires no additional cost or equipment.

In our study, after neostigmine methylsulfate injection, 80% of the patients experienced side effects. All subjects in the R-CMAP group had side effects, and 70% of the patients in the no-R-CMAP group experienced side effects. However, the latter could tolerate PB well. Six patients (12.8%) had side effects to PB treatment. Despite the side effects observed after NT, most patients tolerated PB well. Therefore, side effects after NT are not a good indicator to base decisions regarding PB treatment on. Of the patients in the R-CMAP group who experienced side effects with neostigmine methylsulfate injection, 37.5% were intolerant to PB and 45.8% showed side effects after PB treatment.

MG is difficult to diagnose using MuSK-Ab due to negative results of diagnostic tests such as RNS and NT.<sup>8,24,25</sup> MuSK-Ab analysis is not easy to perform in the clinic, mainly because it is too expensive. AChE inhibitors do not have a therapeutic effect or can worsen MG symptoms in patients with MuSK-Ab.<sup>8,11,15,24,26</sup> In our study, we performed MuSK-Ab detection in 17 patients. Nine patients tested positive. Eight out of the nine MuSK-Ab-positive MG patients were in the R-CMAP group ( $p = 0.015$ , Fisher's exact test). Although we did not perform MuSK-Ab detection for all patients, we believe that an electrophysiological study could detect R-CMAPs after NT in MG patients with MuSK-Ab. Previous studies also suggest that the presence of cholinergic hypersensitivity helps to diagnose MG with MuSK-Ab.<sup>8,10</sup>

This study had several limitations. First, we could not explain female predominance in the R-CMAP group. Second, this study had a retrospective design, a small number of patients and physicians made an arbitrary decision regarding patient selection. Therefore, a selection bias may exist. Third, previous studies applied grading systems using needle electrodes and surface electrodes and modified gain.<sup>7</sup> We used only surface electrodes and normal gain



(5 mV/division). Thus, we might have missed small amplitude R-CMAPs. Further prospective studies are required to support our conclusions.

Our results showed that MG patients with R-CMAPs after NT had a higher frequency of side effects and intolerance to PB treatment. R-CMAP after standard doses of neostigmine may be a good indicator of side effects to PB. Testing for R-CMAPs after a neostigmine injection might help to diagnose MG and develop a therapeutic plan for MG treatment.



## V. CONCLUSION

We investigated the clinical characteristics of myasthenia gravis patients with R-CMAP after NT. Patients in the R-CMAP group had several distinctive features compared with those in the no-R-CMAP group. The R-CMAP group showed a higher frequency of intolerance and side effects to PB. Therefore, we suggest that the presence of R-CMAPs after NT is a good indicator of the side effects of PB, and may help in therapeutic decision making.



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## ABSTRACT(IN KOREAN)

중증 근무력증 환자에서 반복 복합 근 활동전위의 임상적 의의

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이 효 은

반복 복합 근 활동전위는 신경을 자극 시 최초의 복합 근 활동전위 이후 연달아 검출되는 복합 근 활동전위들을 의미한다. 반복 복합 근 활동전위는 선천성 아세틸콜린 분해 효소 결핍, 선천성 느린 통로 중증 근무력 증후군, 유기인제 독성과 같은 질환에서 발견되며 이는 콜린성 신경근육 과민성 상태를 반영한다는 것을 의미한다. 중증 근무력증 환자에서도 아세틸콜린 분해 효소 억제제를 과량 사용하였을 때 반복 복합 근 활동 전위가 나타날 수 있다. 하지만 표준용량의 아세틸콜린 분해 효소 억제제를 중증 근무력증 환자에게 사용하였을 때 반복 복합 근 활동전위는 거의 발견되지 않는다. 반복 복합 근 활동전위의 발생기전은 확립된 바가 없으며 그 임상적 의의에 대해서도 연구된 바가 없다. 그러므로 우리는 표준용량의 네오스티그민주사 이후 반복자극 검사를 시행하였던 환자들에서 반복 복합 근 활동전위의 유무에 따른 임상적 특징에 대해 분석하여 그 임상적 의의에 대해 연구하였다. 총 71명의 환자가 포함되었으며 환자의 의무기록과 전기 생리학적 검사 결과를 검토하였다. 24명에서 표준용량의 네오스티그민주사 이후 반복 복합 근 활동전위가 관찰되었다. 네오스티그민주사 이후 반복 복합 근 활동전위가 발생한 군과 발생하지 않은 군 사이에 질환의 발생 나이, 중증 근무력증 일상생활 수행능력 점수, 추적기간은 차이가 없었다. 반복 복합 근

활동전위가 발생한 군에서 피리도스티그민에 부작용 및 과민반응이 많았으며 최대 복용가능 용량도 적었다. 이 연구를 통해 반복 복합 근 활동전위가 아세틸 콜린 분해 효소 억제제의 부작용과 밀접한 관계가 있음을 확인하였으며 표준용량의 네오스티그민주사 이후 반복 신경자극검사를 한번 더 시행하여 반복 복합 근 활동전위의 유무를 살피는 것이 중증 근무력증 환자의 치료계획 수립에 도움이 될 것이다.



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핵심되는 말 : 중증 근무력증, 반복 복합 근 활동전위, 피리도스티그민

## PUBLICATION LIST

1. Shin HY, Park HJ, Lee HE, Choi YC, Kim SM. Clinical and Electrophysiologic Responses to Acetylcholinesterase Inhibitors in MuSK-Antibody-Positive Myasthenia Gravis: Evidence for Cholinergic Neuromuscular Hyperactivity. J Clin Neurol 2014;10:119-24.

