İSTANBUL ÜNİVERSİTESİ YAYINEVİ

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EVALUATION OF REPETITIVE NERVE STIMULATION WITH DIFFERENT STIMULATION FREQUENCIES IN PATIENTS WITH MYASTHENIA GRAVIS

MYASTHENİA GRAVİS HASTALARINDA FARKLI UYARI FREKANSLARI İLE ARDIŞIK SİNİR UYARIM TESTİNİN İNCELENMESİ

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ABSTRACT

Objective: To investigate the effect of voluntary contraction at low frequency repetitive nerve stimulation (RNS) as a sign of presynaptic compensation in patients with Myasthenia Gravis (MG).

Material and Method: Thirty-five patients with MG were included. RNS at 3 Hz, recorded from the abductor digiti minimi, trapezius, nasalis, and orbicularis oculi muscles were performed. In muscles with more than 10% decrement, RNS at 1 Hz with 20-90 stimuli was applied after 10-second maximal isometric voluntary muscle contraction (MIVMC). Progressive decremental pattern was considered when decrement values were increasing until the last response. Facilitation after MIVMC was determined by dividing the amplitude of motor response in resting state by the amplitude of the motor response recorded just after contraction.

Results: Among 15 patients having RNS at 1 Hz, nine had facilitation after MIVMC. In the muscle with facilitation, there was a significant positive correlation between the increment ratio and the progressive decrement difference between responses 1-4 and 1-9 (correlation coefficient 0.730, p=0.026). Although not statistically significant, muscles showing facilitation following decrement tended to have a progressive decremental pattern.

Conclusion: During RNS, facilitation after MIVMC followed by progressive decremental pattern may be related to presynaptic compensation of neuromuscular transmission failure in MG.

Keywords: Myasthenia Gravis, repetitive nerve stimulation, low frequency stimulation, post-exercise facilitation, decrement

ÖZET

Amaç: Bu çalışmada, Myasthenia Gravis (MG) hastalarında presinaptik kompansasyonun bir göstergesi olarak maksimal istemli kası sonrasında ardışık sinir uyarım testinde (ASU) değişikliklerin incelenmesi amaçlandı.

Gereç ve Yöntem: Otuz beş MG hastası çalışmaya dahil edildi. Bu hastalara abdüktör digiti minimi, trapez, nazalis ve orbikülaris okuli olmak üzere 4 kastan 3 Hz ASU incelemesi yapıldı. Dekrement oranı %10 üzerinde olan kaslarda 10 saniye izometrik maksimal kası sonrasında 1 Hz ASU incelemesi tekrarlandı. Bu kaslarda kası sonrası fasilitasyon ve progresif dekrement paterni varlığı değerlendirildi. Progresif dekrement paterni, ASU incelemesinde dekrement oranının son uyarıya kadar artması olarak belirlendi. Progresif dekrement farkı ise 1-4 ve 1-9 ile 1-4 ve 1-son uyarı ile kaydedilen dekrement değerlerinin birbirinden çıkartılması ile hesaplandı. Fasilitasyon ise kası sonrası ve istirahatte kaydedilen motor yanıt amplitüdlerinin birbirine oranlanması ile belirlendi.

Bulgular: İstemli kası sonrası 1 Hz ASU yapılan 15 hastanın 9'unda fasilitasyon saptandı. Fasilitasyon izlenen kaslarda inkrement oranı ile progresif dekremet farkı (1-4 ve 1-9 uyarı arası) istatistiksel olarak anlamlı pozitif bir korelasyon gösterdi (korelasyon katsayısı 0,730; p=0,026). İstatistiksel olarak anlamlı olmamakla birlikte ilk 9 uyarıda progresif dekrement paterni varlığı dekrementi takiben fasilitasyon izlenen kaslarda daha fazlaydı.

Sonuç: İzometrik kası sonrasında düşük frekanslı ASU incelemesi MG hastalarında presinaptik kompansasyonu gösterebilir.

Anahtar Kelimeler: Myasthenia Gravis, ardışık sinir uyarımı, düşük frekanslı uyarım, egzersiz sonrası fasilitasyon, dekrement

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INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disorder that affects neuromuscular transmission in skeletal muscles (1). The autoimmune process is caused by autoantibodies mostly against acetylcholine receptors (AChR), located at the postsynaptic membrane of the neuromuscular junction (2, 3). Dysfunction of neuromuscular transmission is related to clinical manifestations of muscle weakness that predominate in certain muscle groups and fluctuate in response to fatigue. It is vital to diagnose MG because immunomodulatory and immunosuppressant treatments are available (4).

The diagnosis of MG is based mainly on clinical findings; however, some immunologic and electrophysiologic findings are expected to support the diagnosis (5, 6). Immunologic findings are the presence of antibodies against AChR and muscle specific tyrosine kinase (MuSK) (3). Electrodiagnostic (EDX) tests consist of repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG) (7).

Three Hz RNS is recommended in the diagnosis of MG, and a more than 10% decrement between the first and the fourth motor response indicates failure of neuromuscular transmission with high sensitivity especially in generalized MG (8, 9). Isometric voluntary muscle contraction is performed in the electrodiagnostic evaluation of neuromuscular junction (NMJ) function, in order to detect post-exercise facilitation and exhaustion (8). Post-exercise facilitation is mainly used in the diagnosis of presynaptic neuromuscular diseases such as Lambert-Eaton myasthenic syndrome, as an equivalence for high frequencies of RNS (≥10 Hz) which results in the accumulation of calcium ions in the presynaptic nerve terminal (8, 10). On the other hand, at low frequenciess of RNS, ACh is gradually tapered at each stimuli revealing different types of decremental patterns in diseases with NMJ conduction failure. The decremental pattern showing the most prominent decrease in the amplitude of motor response between the first and fourth or fifth stimuli indicates a postsynaptic transmission defect (8, 11). However, a progressive decremental pattern consisting of a progressive decrease in the amplitude of motor response until the ninth stimuli is related to a defect of ACh release, present in presynaptic transmission (12, 13). By using these data, one might assume that post-exercise facilitation and progressive decrement at low frequenciess of RNS in MG might give some information about the presynaptic ability of ACh release, known as presynaptic compensation of NMJ.

The aim of this study was to investigate the effect of isometric voluntary muscle contraction at low frequency RNS as a sign of presynaptic compensation in NMJ.

MATERIAL AND METHOD

Patients

Patients who were followed in our Neuromuscular clinic between 2015 and 2017 and were diagnosed as having MG were included in the study. The diagnosis of MG was made in the presence of fluctuating muscle weakness clinically when one of the following was present: treatment response to cholinesterase inhibitors or antibodies against AChR or MuSK in sera of the patients (1, 14). All patients were evaluated clinically, using the Myasthenia Gravis Foundation of America (MGFA) scale and the MG Composite scale (8, 9, 15). The clinical response to cholinesterase inhibitors was determined by either clinical examination or the patient's history.

Istanbul University, Istanbul Faculty of Medicine Ethics Committee approved the study (2014/1617, 10.24.2014) and informed consent was obtained from each subject.

Electrodiagnostic tests

The electrodiagnostic (EDX) tests were performed prior to the immunomodulatory or immunosuppressant treatment. Cholinesterase inhibitors were ceased 12 hours before EDX tests (8). In patients who could not tolerate stopping cholinesterase inhibitors for such a long time, tests were performed within the last hour before the subsequent dose. RNS was performed using Medelec Synergy and Keypoint EMG devices (Natus, Inc).

Repetitive nerve stimulation

RNS were recorded from the abductor digiti minimi (ADM), trapezius, orbicularis oculi (OO), and nasalis muscles. Nine stimuli at 3 Hz stimulation frequency were applied to the ulnaris nerve at the wrist, accessory nerve at the neck and facial nerve at the tragus, respectively,

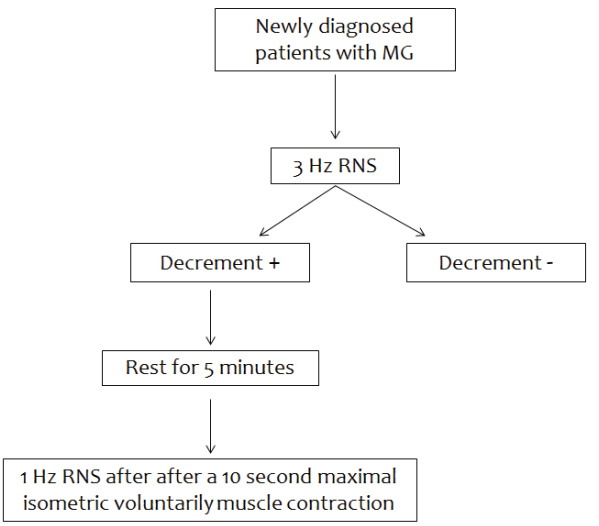

Figure 1: The scheme for electrodiagnostic tests.
MG; Myasthenia Gravis, RNS; repetitive nerve stimulation.

during rest and every minute for 4 minutes after 30 seconds exercise with maximal isometric muscle contraction of the recording muscle. A decrement of more than 10% between the first and fourth motor response was considered as positive (8, 16). If a positive decrement was found, RNS at 1 Hz stimulation frequency was performed with 20-90 stimuli after a 10-second maximal isometric muscle contraction. The decrement between the first and fourth (dec1-4), the first and ninth motor response (dec1-9), and the first and last motor response (dec1-*l*) were calculated. The changes in decrements (Δdec*l-4*) were calculated by subtracting (dec1-*l*) from (dec1-4) and Δdec9-*4* were determined by subtracting (dec1-9) from (dec1-4) (12). A positive Δdec indicates that motor responses continue to decline after the fourth response, whereas a negative result or zero value indicates that motor responses increase or remain unchanged. RNS studies with different stimulation frequencies were applied with a resting period of at least 5 minutes (Figure 1 and 2). The increment ratios were also calculated by dividing the amplitude of the motor response in the resting state by the amplitude of the motor response recorded just after a 10-second maximal isometric voluntary contraction multiplied by 100.

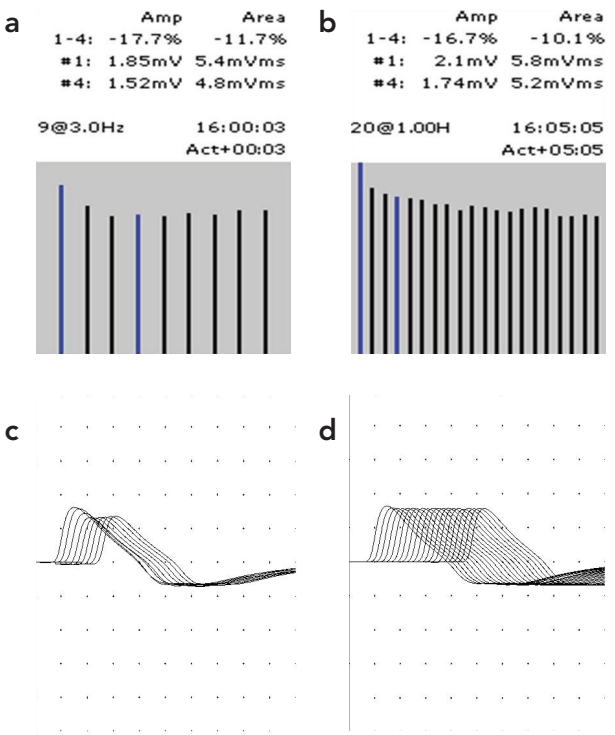

Figure 2: Repetitive nerve stimulation (RNS) tests with different stimulation frequencies. a and b shows RNS recorded from the orcibularis oculi muscle using 3 Hz RNS and 1 Hz RNS after 10-second maximal voluntary isometric muscle contraction, respectively. Compound muscle action potential amplitude increase in b (2.1 mV) compared with a (1.85 mV), showing facilitation and a progressive decremental pattern after exercise. RNS shown in c and d were recorded from the trapezius muscle using 3 and 1 Hz stimulation frequencies, respectively, without facilitation and decrement.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 21.0). Presence of Δdec was compared using the Fisher's test between patients with and without facilitation ($p \leq 0.05$). Correlation analyses between increment ratios and Δdec values were performed using the Spearman's rank test.

RESULTS

Thirty-five patients with newly diagnosed MG were recruited to the study. The clinical features of the patients are summarized in Table 1.

All patients had RNS studies recorded from four muscles. Twenty-eight patients had abnormal decrement in one of the muscles evaluated in RNS studies. Among these patients, RNS at 1 Hz stimulation was performed in 26 muscles of 15 patients. The patients' clinical features, decrement and increment ratios in each muscle are shown in Table 2 and 3. In nine muscles of nine patients, facilitation was seen after a 10-second maximal isometric voluntary muscle contraction. The mean increment ratio was 17.1±9.6 (range, 4-33). Δdec*l-4* was positive in six of

Table 1. Demographic and clinical features of the patients

Age, mean (range)	51.3±16.1 (22-79)	
Sex	**n**	**%**
Female	13	37.1
Male	22	62.9
Mean duration of the symptom onset (month), mean (range)	3.4±2.6 (1-12)	
MGFA	**n**	**%**
I (Ocular)	19	54.3
II (Mild)	8	22.9
III (Moderate)	7	20.0
IV (Severe)	1	2.8
V (intubated)	0	0
Composite score, mean (range)	7.3±7.2 (0-32)	
Serology	**n**	**%**
AChR-ab positive	20	57.1
MuSK-ab positive	5	14.3
AChR-ab negative	5	14.3
Seronegative (AChR-ab and MuSK negative)	5	14.3

AChR-ab, acetylcholine receptor antibody; MuSK-ab, muscle-specific kinase antibody

Table 2. Patients having 1 Hz repetitive nerve stimulation after evaluation of decrement analysis

	Symptom duration (months)	MGFA	Composite score	Serology	Muscle	Decrement-3 Hz(%)
1	3	1	3	AChR-ab +	OO	13
2	3	1	3	AChR-ab -	OO	15
3	2	3b	12	AChR-ab +	OO/Nas/Trapezius/ADM	43/58/15/14
4	6	1	1	AChR-ab +	OO	14
5	2	2b	9	AChR-ab +	OO/Nas	33/23
6	1	1	7	AChR-ab +	OO	43
7	3	1	7	AChR-ab -	OO/Trapezius	17/20
8	3	3b	26	AChR-ab +	OO/Nas	49/72
9	6	1	0	AChR-ab +	OO/Nas	23/11
10	1	1	7	MuSK +	Nas/Trapezius	15/14
11	1	2b	5	AChR-ab +	Nas/Trapezius	15/12
12	1	1	3	AChR-ab +	OO	19
13	2	1	3	AChR-ab +	OO	14
14	1	2b	17	AChR-ab +	Nas/OO/Trapezius	10/17/16
15	2	2b	8	AChR-ab +	OO	60

MGFA, Myasthenia Gravis Foundation of America; AChR-ab, acetylcholine receptor antibody; MuSK-ab, muscle-specific kinase antibody; OO, orbicularis oculi; Nas, nasalis; ADM, abductor digiti minimi

Table 3. Decrement and increment ratios in the studied muscles

Muscle	3 Hz decrement	1 Hz dec1-4	1 Hz dec1-9	1 Hz dec1-*I*
OO	13	-7	0	0
OO	15	8	8	7
OO	43	15	15	15
Nas	58	7	15	23
Trapezius	15	5	5	4
ADM	14	6	6	6
OO	14	7	5	16
OO	33	-5	0	0
Nas	23	0	-4	8
OO	43	11	29	29
OO	17	17	24	27
Trapezius	20	0	0	3
OO	49	0	0	2
Nas	72	28	32	32
OO	23	-12	73	73
Nas	11	5	6	15
Nas	15	2	2	2
Trapezius	14	4	4	4
Nas	15	10	18	19
Trapezius	12	11	8	7
OO	19	9	12	18
OO	14	5	13	22
Nas	10	2	1	1
OO	17	-4	-18	-13
Trapezius	16	5	4	5
OO	60	5	5	18

OO: orbicularis oculi, Nas: nasalis, ADM: abductor digiti minimi

nine muscles (66.7%) showing facilitation, whereas Δdec*l-4* was positive in seven of 17 muscles (41.2%) without facilitation without a statistical significance (p>0.05). A positive Δdec*9-4* was found in four of nine muscles with facilitation (44.4%) and in five of 17 muscles without facilitation (29.4%, p>0.05). The analysis between increment ratio and Δdec*9-4* values showed a positive significant correlation (correlation coefficient 0.730, p=0.026, Figure 3). However, no significant correlation presented between increment ratio and Δdec*l-4*.

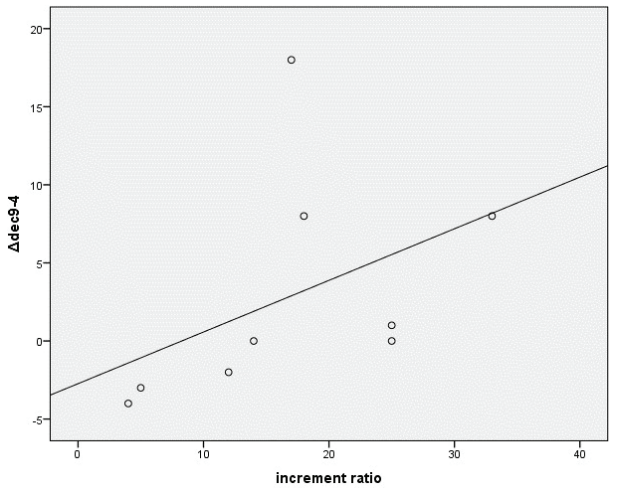

Figure 3: Correlation graph between increment ratio and Δdec*9-4* in patients showing facilitation after 10-second maximal isometric voluntary muscle contraction.

Among nine patients with facilitation after a 10-second maximal isometric voluntary muscle contraction, six had a response to cholinesterase inhibitors, and one patient, with a positive MuSK-ab, did not benefit from cholinesterase inhibitors. In the other two, the response to cholinesterase inhibitors could not be assessed because one was lost to follow-up, and the other had minor symptoms and did not use cholinesterase inhibitors. All six patients who had no facilitation were clinically responsive to cholinesterase inhibitors. Among these six patients, five were AChR-ab positive and one was AChR-ab negative.

DISCUSSION

In electrophysiologic studies, a 10-second isometric voluntary muscle contraction was used to test the presynaptic function of the NMJ (8, 11). A single motor response was recorded just after a 10-second isometric voluntary muscle contraction. An increase in the compound muscle action potential (CMAP) amplitude relative to CMAP recorded at resting is called facilitation, and facilitation of more than 100% is accepted as a presynaptic dysfunction of the NMJ (10). In RNS studies, isometric voluntary contraction of the studied muscle was used to exacerbate the amount of decrement found in the resting state (17-19). The decremental response decreases just after isometric voluntary contraction. After several minutes following the exercise decrement exacerbated, which is called post-exercise exhaustion (17). The mechanism of facilitation and the decrease in decremental response after isometric voluntary contraction was considered to be the accumulation of calcium ions in the presynaptic axon terminal, resulting in increased ACh release through the synaptic cleft (17, 20).

The progressive decremental pattern at 3 Hz RNS was related to a presynaptic NMJ disorder, Lambert-Eaton myasthenic syndrome, and was first described by Baslo et al (12), and confirmed by other studies (13, 21). This finding can be explained as follows: ACh release at low frequency RNS cannot be compensated by secondary and tertiary ACh vesicles in presynaptic NMJ disorders. However, in MG, decremental response starts at second stimulus and becomes most obvious at the fourth or fifth stimulus. From the fifth to the ninth response, the CMAP amplitude stays the same or increases a little (11). This decremental pattern is called a U-shaped or saddle-shaped decrement which is assumed to be related to post-synaptic NMJ dysfunction. In MG, the progressive decremental pattern is not commonly accepted as described above.

In the present study, a progressive decremental pattern was presented in patients with MG, which appears after 10-second maximal isometric voluntary muscle contraction. The progressive decrement after facilitation may possibly be associated with the presynaptic compensation in NMJ, related to an increase in ACh release preceding the accumulation of calcium ions. We hypothesized that the progressive and slow decline during low frequency RNS was an indirect finding of the amount of facilitation after exercise, which could indicate presynaptic compensation in MG. Correspondingly, this kind of compensation would be associated with the response to cholinesterase inhibitors. In this study, we found facilitation after voluntary muscle contraction in nine muscles of nine patients. There was a significant positive correlation between the increment ratio and Δdec*9-4*, but not Δdec*l-4*. This correlation indicates that the more facilitation found in a muscle, the more progressive decrement at 1 Hz RNS. In addition, the progressive decrement until the ninth and last response was found to be more frequent in muscles showing facilitation after 10-second isometric voluntary muscle contraction than those without facilitation; however, these differences did not reach a significant level. These findings could provide some evidence that the mechanism underlying this phenomenon might be associated with presynaptic compensation. In a manner of clinical practice, this electrophysiologic pattern could be tested in a larger number of patients, and its relation with clinical parameters could be investigated in future studies.

The clinical correlation of presynaptic compensation could be linked with a cholinesterase response. However, we found no such relation in our study. The main reason for this might be the small number of subjects in our study. Another reason could be the insufficient muscle contraction. To evaluate facilitation, one should perform a maximal voluntary muscle contraction. Our patients without any treatment and with weakness may not have been able to perform sufficient contraction.

CONCLUSION

During RNS, facilitation after maximal isometric voluntary muscle contraction and progressive decremental pattern might be related with presynaptic compensation in MG.

Ethics Committee Approval: This study was approved by the Ethical Committee of the Istanbul University Istanbul Faculty of Medicine. (2014/1617, 10.24.2014)

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- N.G.Ş, M.B.B., E.K.O., F.D.; Data Acquisition- N.G.Ş, M.B.B., E.K.O., H.D.; Data Analysis/Interpretation- N.G.Ş, M.B.B., E.K.O., F.D.; Drafting Manuscript- N.G.Ş, M.B.B., E.K.O., F.D..; Critical Revision of Manuscript- N.G.Ş, M.B.B., E.K.O., F.D., H.D.; Final Approval and Accountability- N.G.Ş, M.B.B., E.K.O., F.D., H.D., E.O.A.; Technical or Material Support- N.G.Ş, M.B.B., E.K.O., H.D.; Supervision- M.B.B., E.K.O., F.D.

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