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Evoked Electric Responses of the Muscle in Myasthenia Gravis Diagnostics

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Abstract

Analysis of the M-responses parameters of the muscles by means of indirect maximal stimulation with different frequencies is a very important method for diagnostic of Myasthenia gravis (MG). As an indicator of degree of neuromuscular transmission damage, a difference expressed in percents (decrement) between the first- and fifth M-responses was used. To define the dynamic of the release of a neurotransmitter and its interaction with acetylcholine receptor of the postsynaptic membrane in 265 MG patients with 3 imp/sec stimulation in a series of five responses', we have determined the decrement (%) of the size of every following M-responses amplitude in correlation with amplitude of M-response of the previous. 265 MG patients were investigated, out of which 148 (55.9%) were female and 117 (44.1%) were male aged from 10 to 75. MG was diagnosed according to clinical and electromyographic (EMG) data, the level of antibodies against Acetylcholine receptors (AChR), Titin and MuSK, and results of pharmacologic tests. CT of chest was done to reveal pathology of the thymus. The most significant decrement of the M-responses at 3 imp/sec stimulation in a series of five responses was found between the second- and the first M-responses and between the third- and second responses. These data correlate with classically evaluated decrements between the first- and the fifth responses ($r=0.64$; $p<0.001$). The difference between the fifth- and the fourth M-responses was minimal. Thus, during the stimulation, the efficiency of released neurotransmitter interaction with receptors gradually decreases until the third impulse, when the physiologic decrement of neurotransmitter release takes place but from the fourth impulse mobilization of neurotransmitter begins. It is characterized for Lambert-Eaton myasthenic syndrome (LEMS) that as a response to the fourth and fifth stimulus, M-response amplitudes (area) continue to decrease compared with the third- and the fourth M-responses, while this difference is minimal in MG, and all these indicate to the differences in character between the neurotransmitter release and its interaction with AChR of postsynaptic membrane in different synaptic diseases, and this will facilitate to determine the character of the synaptic damage.

Keywords

M-Response, Negative Phase Amplitude, Area, Duration, Neuromuscular Transmission, Post-Tetanic Facilitation, Post-Tetanic Depression, Myasthenia Gravis, Antibodies Against Acetylcholine Receptors (Achr), Titin and Musk

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1. Introduction

The clinical hallmark of MG is fluctuating, painless weakness of muscles that most often affect extraocular, lower bulbar, or limb musculature. Among other diseases the differential diagnosis of MG includes disorders, which affected neuromuscular junction, such as LEMS. The theraphy of these diseases is different. Predicting the probability of successful treatment for the patient assumes that the physician has made an accurate diagnosis. It is ascertained that to determine the pathogenesis of disease lead to correct diagnosis. The aim of the study is to define the characteristic EMG features for MG which differenciated from LEMS which will help the timely diagnosis of MG.

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Diagnostics of MG is made frequently according to the patient's anamnesis and clinical indices. However, even in a case of routine course of the disease, diagnosis should and must be verified by electrophysiological investigation of the neuromuscular transmission. The wide spectrum of EMG investigations is used in the MG diagnosis. The priority in these investigations is given usually to the muscle evoked responses (M-responses) and to the dynamics of their alterations during indirect supramaximal stimulation at different frequencies, applied to the muscle.

2. Materials and Methods

Totally 265 MG patients were investigated – 148 (55.9%) female, 117 (44.1%) male. Age variation - from 10 - 75 years. The diagnosis was based on medical history, clinical – EMG, immunological and mediastinal CT scan data. CT of chest was done to reveal pathology of the thymus. There were revealed thymoma in 17 MG patients (about 16.3 %). EMG study was conducted on the electromyograph Medtronic. The indirect repetitive stimulation of muscles was generated on low (3 imp/sec) and high (50 imp/sec) frequencies. The posttetanic phenomena was studied after 5 seconds (posttatanic alleviate) and 2 minutes (posttetanic exhaustion). In 3 imp/sec frequency stimulation in the series consisting of 5 impulses, every following M-responses amplitude was compare with the previous and the size of the decrements was determined.

Antibodies against Titin, MuSK and AChR was determined in the patients' blood plasma. Thymus gland pathology was revealed by mediastinal CT study.

In the muscles of each myasthenic patient, which have shown the strength deficit, the M-response parameters have been compared to the strength indices, which, in turn, were evaluated by the 6-score scale (0-5) system. Standard clinical electromyograph (Medtronic "Keypoint", USA) was used as a measuring apparatus. Two stimulating parameters were used throughout the experiments – the low frequency stimulation (LFS) – 3 impulses per second, and high frequency stimulation (HFS) – 50 impulses per second. Numerical data obtained have been evaluated according to the students *t* – criterion.

3. Results

According to our data, the mean value of the distal muscles' M-responses in 265 MG patients and healthy subjects does not differ from each other. In MG patients the 5th finger extensor muscle's M-response's mean amplitude was 9.8±1.1 mV (In the healthy subjects it was 8.9±3.4 mV). In a case of significant deficit of the strength in some muscles, the M-response amplitude was decreased, while in some patients, even in a case of significant clinical damage to the muscles, the M-response parameters remained within the normal margins. In a course of the previous investigations it was found, that in MG, a mean amplitude index of the M-response, elicited by a single supramaximal stimulus, does not exceed the normal one found in healthy subjects [1-7, 9-10, 12-13, 15]. It was shown however, that significant damage to the muscle may induce decrease of the M-response as well [1, 8, 14, 16].

It was found that in 15 % of clinically damaged muscles the amplitude of the M-response was decreased, in 21 % - area, and in 8% duration of the negative phase was increased ($P<0.05$). At the same time, correlation between the negative phase of the M-response and the volume of muscle strength was direct ($r=57$, $P<0.001$), while correlation between the negative phase duration and the muscle strength was inverse (r-0.46, $P<0.001$).

According to the reference data, decrease of the M-response amplitude is observed in those muscles only, in which, during low-frequency stimulation, significant block of the neuromuscular transmission is evident [1, 5]. Comparative analysis between the M-responses' parameters and the amplitude (area) decrement in the same muscles' M-responses, elicited by the LFS, and between their initial amplitude values, has revealed reliable inverse correlation ($r=0.64$, $P<0.001$, and $r=0.61$, $P<0.001$ respectively). The M-response amplitude decreased more frequently in the proximal group of muscles than in the distal ones, which indicates that in MG the proximal muscles primarily suffer clinical damage and decrement in them, during the LFS, corresponds to a higher degree.

Hence, decrease of initial amplitude of the M-response and extension of its negative phase in MG, during decreased strength in the tested muscle and at LFS coincides with increased decrement of the M-response amplitude (area). These points not only at elimination of some fibers' potentials from the overall M-responses, but, in turn, also may be due to the path-morphological changes in the neuromuscular synapses.

Administration of an adequate dose of Proserine resulted in increased amplitude of the M-responses in 70.5% of proximal-, and in 65.2% of distal muscles of the MG patients. Well-expressed inverse correlation was found between the initial amplitude of the M-response and its increase after Proserine administration.

Administration of the anticholinesterase drugs elicited increase of the M-response amplitude in 5-15% of distal-, and in 20-40% of proximal muscles, which points at certain quantity of muscle fibers eliminated from the activity in the

MG patients.

Traditionally the volume of the neuromuscular transmission deterioration is analyzed at LFS (3 imp/s) according to the percent ratio (decrement) between the first and fifth M-response amplitudes. If the value of decrement is over 10%, it verifies the neuromuscular transmission deterioration. According to our own-, as well as the reference data [2-5, 10, 11, 12], the value of the M-response amplitude (area) decrement, during LFS, is directly proportional to the muscle damage value. If the mean strength of the muscle tested, during the low-frequency stimulation, scored 4 points, decrement amounted to 18.5±3.2%, while during scoring the strength at an average of 2 points, decrement reached 36.6±11.5% ($P<0.001$).

Considering the predominant malfunction of the proximal muscles characteristic of MG, comparison of the decrement values in 265 MG patients' proximal and distal muscles has shown that in deltoid muscles it made 54.6±13.6% while in the clinically less deteriorated abducent muscles of the 5th finger, it made 15.1±4.5%. Out of 265 patients, in 78 (29.4%), regardless of the malfunction volume in the 5th finger abductor digiti minimi muscles, at LFS, depression of the M-response was not found, while testing of the deltoid muscles in the same patients, has revealed about 30-40% decrement of the M-response amplitude.

Deterioration of the neuromuscular transmission during MG, as a result of the anticholinesterase drugs' adequate dose administration has a reversible character which is manifested in the tested muscles' strength elevation and decrease of the amplitude decrement of LFS. If, before Proserine administration the M-response amplitude's decrement in the deltoid muscles made 54.3±13.6%, after the drug administration is decreased to 32.5±15.9%, while in the abductor digiti minimi muscles of the 5th finger the decrement difference before-, and after the Proserine administration comprised 11.2±0.9%.

In a case of different grade decrements in the MG patients, evaluated with traditional methods in the 5th finger abducent muscle, in the LFS paradigm, series of five impulses were studied and every other M-response amplitude decrement was compared to the previous response amplitude (that first M-response amplitude considered as 100%). This observation allowed to reveal dynamics of the neurotransmitter release or its interaction with the cholinergic receptors in the postsynaptic membranes. The data obtained are shown in Table 1.

Table 1. The M-responses' decrements in the fifth finger abducent muscle, in myasthenic patients. Stimulation rate – 3 imp/sec.

Clasically evaluated decrement, %	Mean values ± between initial M-responses (%),	standard and following at 3 amp/sec	deviation of responses in stimulation	difference series of five
M1-M5	M1-M2	M2-M3	M3-M4	M4-M5
20-30	9.1±1.4	8.5±1.7	5.8±1.3	1.0±0.7
30-40	13.8±2.0	11.3±2.1	5.6±1.6	2.5±0.6
40-50	30.0±2.45	20.8±2.9	2.0±0.5	0.5±0.2

As evidenced by our investigations, in a five impulse series, the most significant decrease of the M-response was found in the second response against the first one, and in the third response against the second one. Difference between the fourth and third responses decreased, while between the fourth and fifth M-responses difference was negligible. At the same time, the direct correlation was found between the differences revealed in the first vs. second, and second vs. third, M-responses and classically assessed decrement between the first and fifth responses ($r=0.64$, $P<0.001$).

Therefore, in MG, efficiency of the released neurotransmitter interaction with the cholinoreceptor decreases progressively till the third response (which coincides with physiological decrement of acetylcholine) while beginning from the fourth response mobilization of the neurotransmitter does occur. Examination of the M-responses' difference between each response of the series against the previous one, in percent values, provides for assessment of the synaptic transmission deterioration character.

The next step following analysis of the neuromuscular transmission, the high-frequency testing of the muscle is a case. The HFS, in the majority of MG patients (80%), results in the M-response amplitude decrement; rarely an increment may be observed. In this case alterations of the M-response amplitude depend not only muscular fibers' inclusion or exclusion in the activity, but on synchronization of the separate muscular fibers' potentials (on the background of unaltered area), decrease of the M-response duration and increase of its amplitude, i.e. pseudofacilitation are observed [5]. Desynchronization is characterized by the M-response amplitude decrease and increase of its duration (area being still unaltered). According to our data, at HFS of the fifth finger abductor digiti minimi muscle, decrement of the M-response amplitude (15-88%) was observed in 84% of the myasthenic patients, in 7.7% of the patients the pseudofacilitation – increment- of the M-response amplitude was found, while in 8.2% of the patients amplitude of the M-response did not change at all.

Immediately following cessation of titanic stimulation in 90% of the patients a post-tetanic facilitation was observed, which should be due to the activation of synaptic transmission and

increased volume of intracellular calcium in the acetylcholine releasing terminal regions, as a result of each incoming nervous impulse. Development of these processes cannot occur without the neurotransmitter mobilization. Degree of facilitation is judged by comparison of the M-responses' amplitudes (areas), elicited by the LFS, before the tetanization and on the background of post-tetanic facilitation, several seconds after tetanization.

Degree of post-tetanic facilitation depends of the initial level of reliability factor in the neuromuscular transmission. In the muscles with the initially low M-response amplitudeand significant decrement, post-tetanic stimulation at the LFS, induces a sharp increase of the M-response amplitude (area), and decrease of the decrement , while in a case of even a slight decrease of the reliability factor, the post-tetanic facilitation occur insignificantly [6].

According to our data, an average increase of the M-response amplitude elicited by the post-tetanic facilitation about 1.5-times exceeded the response enhancement, in the same muscle, elicited by the adequate dose of Proserine administration. The neuromuscular transmission reliability factor increases in both Proserine administration- and post-tetanic facilitation periods.

Post-tetanic facilitation is accompanied with the post-tetanic exhaustion phase, which depends on the titanic stimulation duration and is due to decreased release of acetylcholine from the nerve terminals. The post-tetanic exhaustion is judged by comparison of M-responses' amplitude- and decrement values, recorded at the LFS, 2-3 minutes after the tetanization and those recorded before the tetanization. According to the reference data post-tetanic exhaustion was found in 50-75% of the myasthenic patients [8, 15]. In our experiment, in a paradigm when 3 minutes following titanic stimulation (50 imp/sec) the low frequency stimulation (3 imp/sec) was tested, decrease of the M-responses' amplitude was found in practically all the myasthenic patients, even in those, who had clinically intact muscles and no initial block of the neuromuscular transmission was evident. This latter finding makes the above phenomenon very versatile means for the diagnosis of myasthenia.

4. Discussion

The analysis of 265 MG patients M-response parameters revealed that distal muscles' average indication of the M-response amplitude (area) does not differ from healthy individuals and MG patients. 15% of MG patients with clinically damaged muscles showed decreased M-response amplitude and 21% - area. In 8%, negative phase duration was increased ($p<0.05$). Direct correlation was shown between M-response negative phase amplitude and the strength of the muscle; indirect correlation was observed between M-response negative phase duration and muscle strength. The M-response amplitude of the proximal muscle was decreased more commonly than in the distals, which correlates with more common clinical damage of proximal muscles and high decrement during the stimulation with 3 imp/sec frequency in it. Our results corresponds with Desmedt an Borrestains (1977) data according to which the reduced M-response amplitude is revealed itself in the muscles, where a repetitive stimulation with 3 imp/sec shows high percent of decrement, which points to the damage of neuromuscular transmission; The above indicates not only to the exclusion of certain groups of muscle fiber potentials, but their activity desincronisation as well, which is due to structural changes in the postsynaptic membrane [14].

The increase of M-response amplitude due to the input of adequate doses of Acetylcholinesterase inhibitors in MG patients, indicates to the shutting of the muscle fibers.

The stimulation of 265 MG patients with 3 imp/sec frequency consisting of a series of 5 stimulus and the analysis of the decrement of every next M-response amplitude (area) compared with the previous revealed different regularities in MG patients in comparison with LEMS. In particular, in MG a significant decrement is revealed in the 2^{nd} - 1^{st}, and 3^{rd} - 2^{nd} responses, while between the 3^{rd} - 4^{th} and 4^{th}-5^{th}, the difference is minimal. In LEMS, the decrement is revealed in all five impulses [14, 17].

All these indicate to the differences in character between the neurotransmitter release and its interaction with AChR of postsynaptic membrane in different synaptic diseases, and this will facilitate to determine the character of the synaptic damage. All the above indicates the significance of different treatment of various synaptic diseases.

During tetanic frequencies the M-response reveals parallel processes: the increase of mediator release, the increase of its synthesis and the transmission from the reserve to the prepared fraction of immediate release and the facilitation of the deployment of mediators. Stimulation with high frequencies changes the function of every circle of the neuromuscular junction: Acetylcholine secretion from the presynaptic membrane increases, the supplies of mediators decreases, the synthesis of Acetylcholine and mobilization increases, and Acetylcholine is easily removed from the terminals.

According to our data, in 84% of MG patients, during high frequency stimulation, the range of decrement of M-response amplitude was from 15% to 88%. After 2 minutes from tetanization, stimulation with 3 imp/sec revealed the decrement in every patient, even in clinically non-damaged muscles, where the initial block was not revealed. The

analysis of the 1st and 5th M-response areas shows that despite the decrease of the 1st M-response amplitude, its area equals to the initial M-response area, or is slightly above it, which is connected to the increase of the 1st M-response duration in post-tetanic period which is caused by the desynchronisation of the muscle fiber activity and the decrease of their summation.

All the above mentioned, EMG varieties give us opportunity to differentiate MG from other synaptic diseases.

5. Conclusion

Thus, we have revealed the specific features characteristic for MG M-response parameters, which will contribute to the independent understanding of pathogenesis in synaptic diseases, which, on its behalf, will indulge the timely diagnosis and effective treatment.

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