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THE PROGNOSTIC VALUE OF DIAGNOSTIC TOOLS IN PATIENTS WITH SEROPOSITIVE MYASTHENIA GRAVIS: A RETROSPECTIVE STUDY OF 31 CASES

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Ключевые слова: *серопозитивная миастения, декремент-тест, электромиография единичного мышечного волокна*

Abstract. The prognostic value of diagnostic tools in patients with seropositive myasthenia gravis: a retrospective study of 31 cases. Gryb V.A., Tretyakova A.I., Titov I.I., Chudovska L.D., Nasonova T.I., Slobodin T.M., Doroshenko O.O. *To confirm the diagnosis of myasthenia gravis (MG), in addition to clinical observation of the muscle weakness dynamics, pharmacological and functional tests, Computed tomography/Magnetic resonance imaging (CT/MRI) of the mediastinum, detection of antibodies to acetylcholine receptors (AChR) and to muscle specific tyrosine kinase (MuSK)/; electrophysiological tests are used: rhythmic nerve stimulation (RNS)/decrement test and electro-myography of a single muscle fiber (single-fiber EMG (SF-EMG)/jitter). The aim of our study is to determine the possible relationship between the level of antibodies to AChR and the decrement test value, to verify a correlation between SF-EMG and the severity of MG seropositive to AChR. To evaluate the effectiveness of pathogenetic treatment and prediction of the duration of remission according to the results of the study. A total of 31 patients with myasthenia gravis seropositive to AChR were examined, among whom there were 19 (61.3%) women aged 19 to 74 years. The pattern of muscle weakness was evaluated by a score of the International Clinical Classification of Severity of Myasthenia gravis scale (MGFA). The presence of respiratory failure and its degree was assessed by spirography. The number of antibodies to AChR was determined using enzyme-linked immunosorbent assay (ELISA). The criteria for inclusion in the study were the confirmed diagnosis of seropositive myasthenia gravis with an AChR antibody level of more than 0.5 nmol/L. All patients underwent electrophysiological studies. Patients were examined three times: 1) at the time of visiting the doctor (in the hospital or on an outpatient basis); 2) in 16 and 3) in 24 weeks from the start of the study. Depending on the clinical condition of the patients the following treatment was prescribed: pyridostigmine, methylprednisolone, azathioprine. Statistical analyses were performed using the statistical computing environment R (R Core Team). In the dynamics of observation, a decrease in the level of antibodies to AChR and an improvement in the condition of patients according to the MGFA classification were generally observed but no correlation was found between the severity of MG and the level of antibodies to AChR during the first visit (Kruskal-Wallis test: H (4,*

N=31)=2.23 p=0.69); during the second visit (Kruskal-Wallis test: H (5, N=31)=9.44 p=0.09), as well as during the third visit (Kruskal-Wallis test: H (2, N=30)=2.74 p=0.25). A correlation was found between the concentration of antibodies to AChR and a thymectomy in the clinical history (Kruskal-Wallistest: H (1, N=7)=3.153752 p=0.07): over time, the level of antibodies decreased. Decrement test deviations were detected in 23 (74.2%) of the 31 patients, SF-EMG – in 20 (95%) of 21 patients. Abnormal jitter was recorded in 100% of cases with a generalized form of myasthenia gravis. During all three visits, a correlation was determined between the highest decrement test of symptomatic muscle and MG severity according to MGFA (r=0.39; p=0.042), (r=0.35; p=0.048), (r=0.41; p=0.039); and also between the jitter value and MG severity (r=0.54; p=0.032) (r=0.35; p=0.048), (r=0.61; p=0.034 respectively). Analysis of the contingency tables using the exact Fisher test provided information on the best method of treating patients. We consider that the most effective prognostic test that may affect the choice of further treatment is SF-EMG. However, due to the difficulties of using this method in routine practice, rhythmic nerve stimulation (RNS) test in clinically weak muscles should be recommended. It is not recommended to monitor antibodies to AChR in order to predict the course of the disease, it is better to use this test only for the diagnosis of seropositive myasthenia gravis.

Реферат. Прогностичне значення діагностичних тестів у хворих на серопозитивну міастенію. Гриб В.А., Третякова А.І., Тітов І.І., Чудовська Л.Д., Насонова Т.І., Слободін Т.М., Дорошенко О.О. *Для підтвердження діагнозу міастенії (MG), крім клінічного спостереження динаміки слабкості м'язів, фармакологічних та функціональних проб, комп'ютерна томографія/магнітно-резонансна томографія (КТ/МРТ) середостіння, виявлення антитіл (АТ) до ацетилхолінових рецепторів (AChR) та до м'язової специфічної тирозинкінази (MuSK), застосовують електрофізіологічні тести: ритмічну стимуляцію нерва /декремент-тест/ та електроміографію поодинокого м'язового волокна (single-fibre EMG (SF-EMG) /джиттер/). Мета роботи – визначити можливий зв'язок між рівнем АТ до AChR, даними декремент-тесту, SF-EMG та ступенем тяжкості MG, серопозитивної до AChR, а також можливість оцінки ефективності патогенетичного лікування і прогнозування тривалості ремісії за результатами даних досліджень. Обстежений 31 пацієнт із міастенією, серопозитивною до AChR, серед яких було 19 (61,3%) жінок у віці від 19 до 74 років. Патерн м'язової слабкості оцінювали за шкалою Міжнародної клінічної класифікації тяжкості міастенії (MGFA). Проводили спірографію для виявлення ступеня дихальної недостатності. Кількість АТ до AChR визначали за допомогою імуноферментного аналізу (ELISA). Критерієм включення в дослідження був установлений діагноз серопозитивної міастенії з рівнем АТ до AChR більше 0,5 нмоль/л. Усім хворим було проведено електрофізіологічне дослідження. Хворих обстежували тричі: 1) при зверненні до лікаря (у стаціонарі або амбулаторно); 2) через 16 та 3) через 24 тижні від початку дослідження. Залежно від клінічного стану пацієнтам призначали лікування: піридостигмін, метилпреднізолон, азатіоприн. Статистичну обробку результатів дослідження проводили за допомогою комп'ютера з програмним середовищем статистичних розрахунків «R». У динаміці спостереження в цілому відмічали зменшення рівня АТ до AChR та покращення стану хворих за класифікацією MGFA, але не було виявлено залежності (кореляції) між ступенем тяжкості міастенії та рівнем АТ до AChR на першому візиті (Kruskal-Wallis test: H (4, N=31)=2,23 p=0,69); на другому візиті (Kruskal-Wallis test: H (5, N=31)=9,44 p=0,09), а також на 3-му візиті (Kruskal-Wallis test: H (2, N=30)=2,74 p=0,25). Виявлено зв'язок концентрації АТ до AChR та тимектомії в анамнезі (Kruskal-Wallis test: H (1, N=7)=3,153752 p=0,07): з часом рівень антитіл зменшувався. Відхилення декремент-тесту були виявлені у 23 (74,2%) з 31 хворого, SF-ЕМГ – у 20 (95%) з 21 пацієнта. Аномальний джитер реєстрували в 100% випадків генералізованої форми міастенії. На всіх трьох візитах було встановлено кореляційний зв'язок між показником найвищого декремент-тесту симптомного м'яза хворого та ступенем тяжкості MG за MGFA (r=0,39; p=0,042), (r=0,35; p=0,048), (r=0,41; p=0,039); між значенням джитера та ступенем тяжкості MG за MGFA (r=0,54; p=0,032) (r=0,35; p=0,048), (r=0,61; p=0,034) відповідно візитам. Результати аналізу таблиць спряженості з використанням критерія Фішера дали змогу інформувати про найкращий метод лікування досліджуваних пацієнтів. Найефективнішим прогностичним тестом, що впливав би на вибір подальшої тактики лікування, вважається SF-EMG, але враховуючи складність і затратність його проведення, можна рекомендувати ритмічну стимуляцію в симптомних м'язах. Не рекомендується проводити моніторинг АТ до AChR з метою прогнозу перебігу захворювання, а використовувати цей тест тільки для встановлення серопозитивної міастенії.*

Myasthenia gravis (MG) is the most common autoimmune disease associated with the production of antibodies to the structures of the neuromuscular junction which is based on the destruction of acetylcholine receptors by factors of humoral and cellular immunity. Myasthenia gravis is classified as a disease mediated by B-cells depending on the balance of T-cell concentration [10].

Diagnosis of MG is primarily based on clinical observation of skeletal muscle weakness dynamics.

The diagnosis is confirmed by:

1. Testing of blood serum for the presence of known myasthenic autoantibodies: antibodies to nicotinic acetylcholine receptors (AChR) and to a specific enzyme – muscle specific tyrosine kinase (MuSK).

2. Electrophysiological tests, including rhythmic nerve stimulation (RNS) /decrement test/ and electromyography of a single muscle fiber (single-fiber EMG (SF-EMG) /jitter/).

3. Inhibition of acetylcholinesterase using a pyridostigmine test or ice pack on the eyes, usually improves symptoms [8, 15].

After the diagnosis of MG, a search for a possible cause is carried out, i. e., CT/MRI of the mediastinum is performed to identify thymoma.

In patients with double seronegative MG, i. e., in the absence of antibodies to AChR and MuSK, the spectrum of autoimmune synapse targets also includes agrin, protein 4, that is associated with low-density lipoprotein receptors (LRP4) and collagen Q, as well as a number of postsynaptic structures, in particular transcription factor SOX1, muscle protein titin, ryanodine receptors (RyR).

The presence of antibodies to these structures is associated with thymoma in patients under 60 years of age or is observed in individuals with late onset of MG without thymoma [17].

Since antibodies to agrin and its LRP4 receptors can also occur in amyotrophic lateral sclerosis [2], and antibodies to titin in rheumatoid arthritis, systemic lupus erythematosus [17], it is still not clear how specific these antibodies are to myasthenia gravis. Antibodies to transcription factor SOX1 are markers of paraneoplastic syndrome (including Lambert-Eaton syndrome) [6].

According to the guidelines of the British Neurology Association, Myasthenia Gravis Association-UK [8], neurophysiological tests can help establish a diagnosis in seronegative patients with suspected MG.

Repeated rhythmic stimulation of nerves (decrement-test) is the initial mandatory test; in a negative result SF-EMG should be considered which has low specificity and can be positive in a wide range of other processes such as denervation and myopathic disorders but at the same time the most sensitive technique in detecting the reliability of neuromuscular junctions (NMJ) [14].

Patients with MG should be managed by an experienced neurologist, preferably working in a large neuromuscular centre with critical care support, who provides adequate assistance in exacerbation and prevention of these exacerbations, predicts the course of the disease. This is also important for special situations, such as pregnancy and delivery, as patients often suffer relapses in the puerperium.

The following questions demand answers:

1. Is it possible to determine the severity of MG by the level of antibodies to AChR / MuSK or according to electromyography?

2. Is it reasonable to predict the course of the disease to continue or replace immunosuppressive therapy?

3. Is it possible to prevent exacerbation in pregnant women with MG by rapid immunomodulation, i.e., by the introduction of human immunoglobulin?

Some studies have shown that determining the concentration of antibodies to an antigenic target in myasthenia gravis, in particular AChR, can be not only an additional diagnostic criterion for this disease but also serve as a source of information. This information makes it possible to predict the course of the disease and objectify the suppression of autoimmune aggression with an assessment of the reliability of the achieved remission with adequate pathogenetic therapy [5].

Other authors believe that the absolute titer of antibodies to AChR is not related to the severity of MG, the presence or absence of thymoma, to the sex, age, and duration of the disease [15, 17]. However, this indicator may be a useful marker for inadequate immunotherapy [13].

SF-EMG is currently recommended for diagnosis and monitoring of MG but this technique has a less enroll in daily clinical practice outside academic institutions. Repetitive nerve stimulation (RNS) is not as sensitive as SF-EMG but it is the most widely used electrodiagnostic method in the evaluation of suspected neuromuscular transmission disorders. RNS is technically easier and does not require specialized technical training and skill as SF-EMG. Repetitive nerve stimulation was first used by Jolly in 1895.

There are data on the number of deviations during low-frequency RNS in patients with MG. According to report of Chen Y.P. et al. [4] from large Center for Myasthenia Gravis in Beijing, China, they analyzed the positive rates of RNS in 436 MG patients and compared the abnormalities in different nerves including facial, accessory, axillary and ulnar nerves.

Among them, 73.85% had abnormal recordings on low-frequency RNS test. The highest abnormality was in facial nerves (82.30%), then axillary nerves (52.17%) and the lowest – in ulnar nerves (27.64%).

The positive rates of RNS in ocular MG were significant lower than those in generalized MG patients. And there were no significant statistical differences of RNS abnormal rates in types IIa, IIb, III and IV MG patients with 89.66%, 82.56%, 91.67% and 83.33%, respectively.

In ocular MG, 16.34% patients were positive in RNS test in the stimulation of accessory, axillary and ulnar nerves. And 79.50% patients with generalized MG had two or more nerves with abnormal results.

As noted by Baruca M. et al. [16], it was not yet possible to establish the prognostic significance of lengthening / shortening of jitter depending on changes in the severity of MG. Although, according to the results of their own studies, the authors indicate that there

is a correlation between the deterioration of patients' state and the growth of jitter according to SF-EMG.

Aim of the study: to answer or the following controversion questions:

1. Is there a relationship between the level of antibodies to AChR with the severity of AChR MG?

2. Is there a correlation between the decrement test and jitter with the severity of AChR MG?

3. Is it possible to evaluate the effectiveness of pathogenetic treatment and the stability of remission in this category of patients?

MATERIALS AND METHODS OF RESEARCH

We retrospectively analyzed the clinical course of 31 MG patients who presented with only mild and moderate symptoms; 22 (71%) of them had SF-EMG data. We correlated their SF-EMG results with the severity of their later clinical course.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

A total of 31 patients with seropositive MG underwent standard clinical diagnosis process, including 19 (61.3%) females, ranging from 19 to 74 years with a female-to-male ratio of 1.6:1. The mean age was 47.9±16.9 years. There were 4 females/1 male, up to 30 years old between 30 and 60 years – 11/8 people, over 60 years – 4/3 people respectively.

9 patients were observed and treated in the neurological department of the municipal non-profit enterprise City Clinical Hospital No. 1 of the Ivano-Frankivsk City Council (Ivano-Frankivsk) and 22 patients were observed and treated at the Department of Neurology No. 1 of the P.L. Shupyk National Medical Academy of Post-graduate Education (Kyiv) during 2017-2019.

A thymectomy was performed in 7 (22.6%) patients. Among the concomitant diseases, the most common pathology was the cardiovascular system (38.7%) which corresponds to the general population trend as well as thyroid disease (19.3%). According to Gilhus N.E. et al. [9], thyroid diseases are comorbid for MG.

Following the SF-EMG study, treatment decisions were determined by neurologist. All patients received pyridostigmine. Immunosuppressive medication was given to all patients who do not have a fully satisfactory functional result with symptomatic and supportive therapy alone (77.4%): 57% – corticosteroids (of which 29% – periodically, with worsening condition), 43% – azathioprine.

The pattern of muscle weakness, i. e., the severity and its predominant distribution, was evaluated by a score of the International Clinical Classification of Severity of Myasthenia gravis scale [10]. The presence of respiratory failure and its degree was assessed by spirography ("SpiroComProfessional", Kharkiv) according to the indicator "Forced vital capacity (FVC)": the normal FVC range for an adult is 80% or more, 65-79% – mild manifestations of respiratory failure, 50-64% – medium, less than 50% – severe respiratory failure [1]. The number of antibodies to AChR was determined using enzyme-linked immunosorbent assay (ELISA).

The criteria for inclusion in the study were: the confirmed diagnosis of seropositive MG with an AChR antibody level of more than 0.5 nmol/L. Exclusion criteria: systemic diseases, acute myocardial infarction, acute stroke, purulent focus (abscess), cancer, decompensated somatic diseases, fever.

All patients underwent electrophysiological studies. 10 patients underwent RNS test in the scientific and practical center of electrophysiological research on the basis of the Department of Neurology and Neurosurgery of Ivano-Frankivsk National Medical University on the computer complex "Neuro MEP Micro EMG" (Neurosoft, RF).

Indicators from the weakest muscles (orbicularis oculi, deltoid, extensor digitorum communis) are averaged according to the generally accepted technique. [11]. In addition to the decrement test, 22 patients underwent an SF-EMG jitter study according to individual examination plans at the Department of Functional Diagnostics of the Institute of Neurosurgery named after Academician A.P. Romodanov National Academy of Medical Sciences of Ukraine (Kyiv) on the Neuro-MVP-4 computer complex (Neurosoft, RF).

After signing the informed consent for the study the patients were examined three times:

1) when contacting a doctor (in a hospital or on an outpatient basis), 2) after 16 and, 3) 24 weeks after the start of the study.

7 patients arrived on the second visit earlier than planned: in 3-10 weeks due to worsening of condition. One patient arrived 19 weeks later, 5 weeks earlier than the planned 3rd visit. Depending on the condition of the patients treatment was prescribed according to the protocol [15].

Assessment of MG severity by MGFA, RNS, SF-EMG was performed 4 hours after taking the morning dose of pyridostigmine.

Statistical analyses were performed using the statistical computing environment "R" [11]. The average value and the standard deviation of the studied populations are denoted by M±σ.

We used the Kruskal-Wallis analysis of variance and the median criterion which allow us to compare the values of the characteristics in several

observation groups as well as the Kendall rank correlation coefficient which is one of the nonparametric measures of the characteristics dependence. The choice of non-parametric methods is dictated by the small sample size. Its peculiarity is that it can be used in the case of a small number of observations, even if there are only one such observations.

The Fisher Exact Test for Count Data is implemented using the "R" environment (basic statistical applications) during the second and third visits to determine the effectiveness of treatment according to the relationship between the prescribed regimen and the dynamics of MG severity by the MGFA quantitative score.

RESULTS AND DISCUSSION

At the initial examination of patients according to MGFA the distribution of the disease severity was as follows: Class I – 3 (9.7%), Class IIa – 12 (38.7%), Class IIb – 6 (19.4%), Class IIIa – 3 (9.7%), Class IIIb – 6 (19.4%) (Tabl. 1).

Table 1

Distribution of patients with myasthenia gravis according to the MGFA class during the study

Visit	MG severity							
	without clinical manifestation	I	IIa	IIb	IIIa	IIIb	IVa	V
1	1	3	12	6	3	6	-	
2	3	8	12	4	2	1	-	1
3	7	11	11	-	1	-	-	

The mean duration from initial symptom to definite diagnosis was 50.62±33.30, ranging from 3 to 114 months.

The clinical picture of almost half of the patients (45.2%) was characterized by weakness of the muscles of the trunk and / or proximal limbs with involvement of the bulbar muscles and weakness of the oculomotor muscles of varying severity as well as impaired respiratory function according to the FVC values determined by spirometry.

In addition to pyridostigmine, immunomodulatory therapy with plasmapheresis or human immunoglobulin was prescribed to almost all patients with worsening conditions – 22 patients (70.9%). Immunosuppressive therapy in the form of methylprednisolone was prescribed or extended to 12 patients of 31 (38.7%), azathioprine – 3 (9.7%) patients, combined immunosuppressive therapy (methylprednisolone + azathioprine) was received by 4 (12.9%) patients with a prospect transition after 3 months to monotherapy with azathioprine. 10 patients refused the prescribed immunosuppressive therapy.

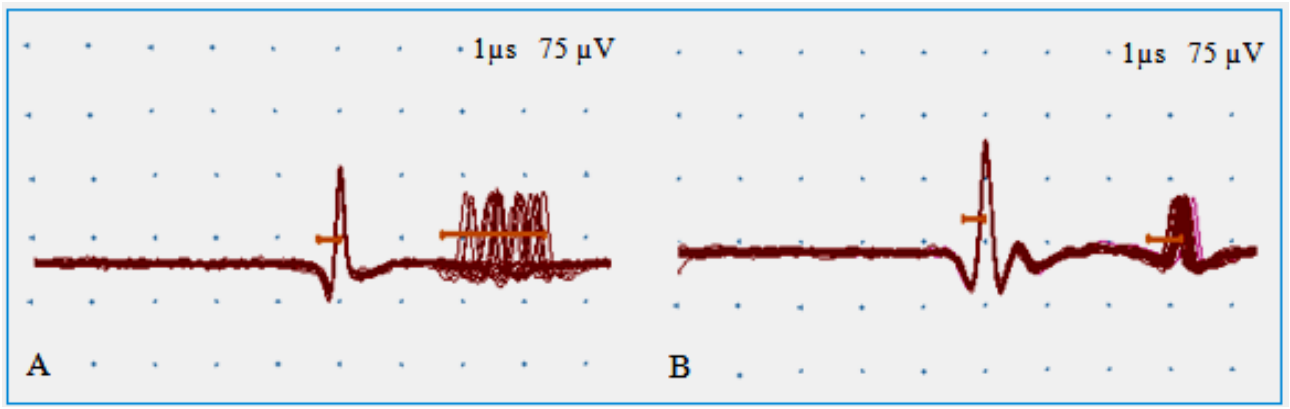
The average AChR antibodies level at the beginning of the study was 18.63±17.20 (minimum 2.4; maximum 78.6) nmol/L. In 93.5% of cases, the AChR antibodies level was not more than 40.0 nmol/L.

RNS deviation was found in 23 of 31 patients (74.2%), SF-EMG – in 20 of 22 (91%) patients. In one case (class I according to MGFA classification) the changes in electrophysiological indicators are not established; abnormal jitter is registered in 100% of generalized form of MG cases.

The indicators of the decrement of M-responses during stimulation with a frequency of 3 Hz depending on the studied muscles are as follows: m. orbicularis oculi – 10.9% (from 3.3% to 23.9%); m. digastricus – 10.9% (from 3.4% to 19.9%); m. trapezius – 14.2% (from 2.3% to 35.7%); m. deltoideus – 18.6% (from 4.3% to 60.1%); m. abductor digiti minimi – 5.9% (from 0.3% to 15.8%).

A weak correlation was found between the high decrement test of the patient's symptomatic muscle and the severity of MG according to MGFA (r=0.39; p=0.042). The maximum values of jitter averaged: in m. orbicularis oculi 75.8±21.5 (minimum 42.4; maximum 96.6) μs; m. deltoideus 164.5±52.5 (minimum 42.4; maximum 201.1) μs; m. extensor digitorum 155.2±49.1 (minimum 51.1; maximum 186.1) μs (Fig.).

A moderate relationship (r = 0.54; p = 0.032) was determined between the jitter value and the MG severity according to MGFA. During the second visit, in 16 weeks, in three patients (9.5%) a complete remission of the disease was recorded, the number of patients with I class of severity according to MGFA almost tripled compared with the previous visit. It is important that cases with mild respiratory failure (IIb class MGFA) decreased from 19.3% during the first visit to 12.9%, and IIIb MGFA during the second visit was only in one patient (first visit – 19,4% of cases, the second visit – 3.2%); while in addition to limb weakness the patient was found to have moderate respiratory failure (FVC – 63%).



Neuromuscular jitter recording orbicularis oculi muscle (shown in a super imposed mode):
(A) Abnormal jitter in a 35-year-old patient with MG (mean consecutive discharge (MCD) =186,1 µs).
(B) Normal jitter in a 52-year-old patient with ptosis (MCD =31.5 µs)

It should be noted that patients with MGFA grade IIb, IIIa, and IIIb established at this visit did not receive immunosuppressive therapy; and they were persuaded to take medication of this group. In general, there was an improvement in the condition of patients, except in one case when a patient with a previous MGFA IIa treated with methylprednisolone 8 mg every other day developed pneumonia and an exacerbation of the disease (MGFA V requiring mechanical ventilation).

Assessing the dynamics of MG severity in each patient, we got the following picture: worsening of the condition occurred in 5 patients (16.1%), a decrease in severity – in 22 (71%), 4 (12.9%) patients remained unchanged. Using Fisher exact test with the "R" program, the relationship between the treatment method (applied medication and treatment regimens) and its results (p=0.048) was revealed. Along with dose adjustment of pyridostigmine, immunomodulating therapy was additionally prescribed for patients with worsening conditions – plasmapheresis or human immunoglobulin.

Immunosuppressive therapy in the form of methylprednisolone was continued in 12 (38.7%) patients, with increasing the dose in four of them, in two – it was reduced; in one patient, the medication was canceled, 6 of 31 patients (19.4%) were additionally prescribed a corticosteroid, 5 (16.1%) patients received azathioprine, three of which canceled methylprednisolone; four patients received methylprednisolone + azathioprine. Three patients (9.7%) refrained from immunosuppressive therapy.

The AChR antibodies level during the second visit was 18.66±21.16 (minimum 1.8; maximum 67.0) nmol/L (p=0.996).

Only one patient had an antibody level above 30.0 nmol/L. In a patient with MGFA V, the AChR antibodies level was 38.0, and during the first visit in MGFA IIa – 78.0 nmol/L.

During the second visit, a weak correlation was also confirmed between the high decrement test score for symptomatic muscle and MG severity according to MGFA (r=0.35; p=0.048). Since the maximum jitter value during the first visit was observed in m. deltoideus, this indicator is taken as a basis. Then the task was set: to estimate the average jitter value for all classes of MG severity during all visits (Tabl. 2).

Table 2

Jitter analysis according to MGFA and visits (M±m)

Visit	MG severity, Number of patients (n = 22)						
	Without clinical manifestations	I	IIa	IIb	IIIa	IIIb	V
1	55.2±11.3	56.8±15.4	98.7±23.6	97.3±24.3	112.3±36.6*/**	136.2±40.1*/**	-
2	65.4±8.4	79.3±32.9	112.9±32.0*	102.3±35.1	117.4±25.0	123.0±16.6*/**	187.5#
3	64.8±12.7	73.4±33.2	123.6±28.4*	-	107.3±16.9	-	-

Notes: * statistically significant difference in jitter between class IIa-IIb and patients without clinical manifestations; ** statistically significant difference in jitter between classes IIIa-IIIb and class I; # statistically significant difference in jitter between class V and classes I-IIIb.

It is noticeable that there is a significant difference in jitter with an increase in the MG severity but a clear relationship is not traced. A moderate correlation was confirmed between the jitter value and MG severity during the second visit (r=0.59; p=0.031).

During the third visit, no patient showed signs of respiratory failure (FVC>80%), i. e., the maximum severity was IIIa according to MGFA classification in only one patient who was not taking immunosuppressive therapy and was ready to do it, IIa – in 12 patients (47%), 11 patients (38.1%) had isolated oculomotor disorders (class I according to MGFA), 7 patients had no complaints, one patient did not appear on the third visit.

The AChR antibodies level during the third visit compared with the second visit was 9.36±7.82 (minimum 0.40; maximum 31.0) nmol/L (p=0.001). In one patient, the antibody concentration was 31.0, and in another 22.0 nmol/L. During the third visit, a weak correlation was also verified between the decrement index of the M-responses from the symptomatic muscle and the MGFA class (r=0.41; p=0.039). A moderate correlation was confirmed between the jitter value and the MG severity according to MGFA (r=0.61; p=0.034) during the third visit.

In the dynamics of observation, in general, a decrease of the AChR antibodies level and an improvement of patients condition according to the MGFA classification were noted but there was no correlation between MG severity and the AChR antibodies level during the first visit (Kruskal-Wallis test: H (4, N=31)=2.23, p=0.69), which was confirmed by the median test (Chi-Square=1.79; df=4, p=0.77). Also, no correlation was found between these indicators during the second and third visits: during the second visit (Kruskal-Wallis test: H (5, N=31)=9.44, p=0.09), confirmed by the median test (Chi-Square =6.97, df=5, p=0.22), and also during the third visit (Kruskal-Wallis test: H (2, N=30)=2.74, p=0.25) and Chi-Square =2.50, df=2, p=0.29, respectively). There was no gender dependence of antibodies to the AChR level (Kruskal-Wallis test: H (1, N=31)= .1819363, p=0.67) and the median test Chi-Square = .3977273, df=1, p=0.53). A correlation was revealed between the concentration of the AChR antibodies level and a thymectomy in the clinical history (Kruskal-Wallis test: H (1, N=7)=3.153752, p=0.07): the level of antibodies decreased over time.

The decrement index of the M-responses from the symptomatic muscle did not reveal a correlation between high decrement values and muscle weakness signs. Although during all three visits, a weak correlation was determined between the high decrement test from symptomatic muscle and MG severity (r=0.39; p=0.042), (r=0.35, p=0.048), (r=0.41; p=0.039), respectively.

The maximum of jitter values averaged: in m. orbicularis oculi 75.8±21.5 (minimum 42.4; maximum 96.6) μs; m. deltoideus 164.5±52.5 (minimum 42.4; maximum 201.1) μs; m.extensor digitorum 155.2±49.1 (minimum 51.1; maximum 186.1) μs. A moderate correlation between the jitter value and MG severity was established during all three observation visits (r=0.54; p=0.032), (r=0.35; p=0.048), (r=0.61; p=0.034).

It has been demonstrated that the obtained results are consistent with the data of Reliability of SF-EMG authors [11], where the sensitivity of electrophysiological tests and a high degree of jitter anomaly in SF-EMG were confirmed, especially in seropositive patients. The authors indicate that the sensitivity of SF-EMG in the diagnosis of MG was 98% (95% CI: 0.94-1.02), while the specificity was 70% (95% CI: 0.54-0.86) with a positive predictive value of 79% (95% CI: 0.74-0.79) and a negative predictive value of 97% (95% CI: 0.94-0.99). I.e., normal SF-EMG results would be unlikely in patients with MG.

Therefore, SF-EMG is considered the best prognostic test that would influence the choice of further treatment tactics but given the complexity and cost of its implementation, RNS in symptomatic muscles should be recommended. We do not recommend monitoring the AChR antibodies level in order to predict the course of the disease but use this test to identify seropositive MG.

Analysis of the contingency tables using the exact Fisher test provided information on the best method of treating patients. The relationship between the prescribed treatment during the first visit and the results obtained during the second visit is weak, not statistically significant (p-value =0.1564). Apparently, there was an effect on the outcome of immunosuppressive therapy rejection in 10 (32.3%) patients. The relationship between the prescribed treatment during the second visit and the observed results during the third visit is strong, statistically significant. The results of calculations by the Fisher criterion: p-value =0.01966.

Therefore, the use of a regimen where azathioprine or glucocorticoid is added to the base pyridostigmine medication makes it possible to significantly increase the treatment effectiveness.

CONCLUSIONS

1. Repeated analyzes of the Acetylcholine Receptor antibodies level for treatment control management in patients with seropositive myasthenia gravis are not recommended.

2. A weak correlation between the maximum rate of decrement according to repetitive nerve stimulation test in the weakest muscles and Myasthenia Gravis severity was observed.

3. Single fiber EMG is the best prognostic test that correlates with the disease severity and affects the choice of further treatment tactics. Due to the difficulties of using this method in routine practice, rhythmic nerve stimulation test in clinically weak muscles should be recommended.

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