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STATE ANXIETY ASSESSMENT IN PATIENTS WITH MYASTHENIA GRAVIS

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182 patients with myasthenia gravis aged 18 to 83 years were examined. Patients were assigned to the class and subclass of myasthenia gravis according to the Myasthenia Gravis Foundation of America, the severity of myasthenia gravis was quantified on the Quantitative Myasthenia Gravis score, and the level of state anxiety was determined on the Spielberger-Hanin test. An immunological test was performed to determine the presence and titer of antibodies to acetylcholine receptors, muscle‑specific receptor tyrosine kinase, and to determine the presence of antibodies against titin and SOX1. The mean level of state anxiety in patients with ocular form of disease was 44.0 (41.0; 48.0) points, which corresponds to a moderate level and does not require correction. The corresponding index in patients with generalized myasthenia gravis was significantly higher and amounted to 53.0 (45.0; 59.0) points ($p < 0.001$), which corresponds to a high level of state anxiety and requires its correction. It was found that the state anxiety level correlates with the age of patients ($p=0.19$; $p=0.008$), clinical form of myasthenia gravis ($p=-0.35$; $p=0.003$), with indices of assessment of the myasthenia gravis severity ($p=0.54$; $p<0.001$), and with the titer of antibodies against acetylcholine receptors ($p=0.46$; $p<0.001$).

Key words: myasthenia gravis, anxiety, antibodies, titin, SOX1, muscle-specific kinase, acetylcholine receptors.

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ОЦІНКА РЕАКТИВНОЇ ТРИВОЖНОСТІ У ХВОРИХ НА МІАСТЕНІЮ

Обстежено 182 хворих на міастенію у віці від 18 до 83 років. Хворим визначали клас та підклас міастенії за класифікацією Myasthenia Gravis Foundation of America, ступінь тяжкості міастенії оцінювали кількісно за шкалою Quantitative Myasthenia Gravis, рівень реактивної тривожності визначали за шкалою Спілбергера-Ханіна. Проводили імунологічне обстеження з визначенням наявності та титру антитіл до рецепторів ацетил-холіну, м'язово-специфічної тирозин-кінази, а також визначали наявність антитіл до титину та SOX1. Середній рівень реактивної тривожності у хворих на очну форму склав 44.0 (41.0; 48.0) бали, що відповідає помірному рівню та не потребує корекції. Відповідний показник у хворих на генералізовану міастенію був достовірно вищим та склав 53.0 (45.0; 59.0) бали ($p<0,001$), що відповідає високому рівню реактивної тривожності та потребує її корекції. Встановлено, що рівень реактивної тривожності корелює з віком пацієнтів ($\rho=0.19$; $p=0.008$), клінічною формою міастенії ($\rho=-0.35$; $p=0.003$), з показниками кількісної оцінки тяжкості міастенії ($\rho=0.54$; $p<0.001$), з титром антитіл до рецепторів ацетилхоліну ($\rho=0.46$; $p<0.001$).

Ключові слова: міастенія, тривожність, антитіла, титин, SOX1, м'язово-специфічна тирозин-кіназа, рецептори ацетилхоліну.

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Myasthenia gravis is a relatively uncommon autoimmune disease of unknown etiology characterized by neuromuscular synapse involvement, mainly due to the response of autoantibodies to acetylcholine receptors (AchR) or to a specific enzyme – muscle-specific kinase (MuSK). As a result, pathological fatigue and skeletal muscle weakness develop, and they are the dominant manifestations of the disease [1, 10–11].

According to epidemiological studies, the incidence of myasthenia gravis ranges from 1.7 to 10.4 cases per 100 thousand population per year, and in the United States it reaches 20 cases per 100 thousand population per year. Despite significant progress in diagnosis and treatment, the prevalence of the disease continues to increase, mainly among the elderly population [5, 7, 9, 10].

Currently, most scientists around the world use the classification of myasthenia gravis according to MGFA (Myasthenia Gravis Foundation of America), according to which there are 5 classes of the disease: Class I –ocular orm; Class II-IV – generalized, respectively – mild, moderate, severe; Class V – generalized, it includes patients requiring intubation and/or artificial lung ventilation. Classes II-IV are divided into 2 subclasses: A – with a predominance of weakness and pathological fatigue of the muscles of the extremities; B – with a predominance of weakness and pathological fatigue of the bulbar and/or orofacial muscles [10]. At the same time, this classification, despite the convenience and ease of use, does not always take into account the individual manifestations of certain symptoms in each individual patient. For a deeper quantification of symptoms, you can use the quantification scale of myasthenia gravis (Quantitative Myasthenia Gravis Scale) [10]. This scale more accurately reflects the degree of clinical manifestations, as well as their dynamics, and can be used to assess the effectiveness of treatment.

Myasthenia gravis, like most chronic diseases, affects the psycho-emotional state of patients. In particular, it can increase anxiety, worsen the quality of life, often lead to professional, social maladaptation, despite the potential curability of most patients and a good prognosis in general. Often, the development of so-called "false compensation" in myasthenia gravis, when patients' complaints do not correspond to objective data on the severity of their condition, is associated with the effects of depression and/or increased anxiety, which should be considered when working with each patient [1, 2, 4, 6, 8, 12–15].

Anxiety is understood as an emotional state characterized by a feeling of increased excitement, often without external causes. Anxiety can develop normally, in addition, it can be pathological, when there is a disorganization of the general human activity due to its development. A distinction is made between state anxiety (SA), which arises as a result of a certain situation or event and can potentially be the object of therapeutic influence, and trait anxiety (TA), which is a personality trait characterized by a persistent tendency to perceive many life situations as threatening. The depth of manifestations of anxiety is mild, moderate (which is the physiological norm, the so-called "useful anxiety") and severe (which requires special attention) [3].

A widespread method of diagnosing the anxiety level is the scale of self-assessment of anxiety level by Ch.D. Spielberger in the modification of Yu.L. Hanin, which allows to assess the level of anxiety at the moment (SA as a condition), as well as TA (as a stable (permanent) personal characteristic) [3].

Indices of reactive anxiety in patients with myasthenia gravis remain insufficiently studied and need to be clarified in order to optimize treatment approaches and improve the quality of life in patients.

The purpose of the work was to study the features of the development of state anxiety in patients with myasthenia gravis.

Materials and methods. 182 patients with myasthenia gravis were examined, including 147 (80.8 %) – patients with generalized form of the disease, 35 (19.2 %) – with ocular form, who were hospitalized in the Department of Neurology No. 1 ME “Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov” or treated on an outpatient basis in the period from 2014 to 2017.

Clinical and neurological examination included collecting complaints, medical history and life, and neurological examination. The MGFA classification was used to assess the clinical form, class and subclass of myasthenia gravis. The severity of myasthenia gravis was quantified on a QMG scale [10].

All patients had their AchR and MuSK antibody levels determined by enzyme-linked immunosorbent assay (ELISA), including quantitatively, and also determined the presence of antibodies to titin and SOX1 by indirect immunofluorescence. These examinations were carried out on the basis of the Clinical and Diagnostic Laboratory of the ME “Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov”.

All patients independently answered 40 questions of the Spielberger–Hanin anxiety self-assessment scale, which are assessed by SA (questions 1–20) and TA (questions 21–40). SA and TA were calculated according to the formulas according to the key for estimating SA and TA. Interpretation of the results was carried out depending on the number of points received: up to 30 points – mild anxiety, 31–44 points – moderate anxiety, 45 and above points – severe anxiety [3].

When checking the conformity of the distribution, the quantitative features did not correspond to the normal law according to the Shapiro–Wilk and Kolmogorov–Smirnov tests with the Lilliefors' test for normality, so the methods of nonparametric statistics were used in mathematical processing. Statistical processing of the study results was carried out using a personal computer with Microsoft Excel software products (Microsoft Office 2016 Professional Plus, Open License 67528927), STATISTICA 6.1 (StatSoftInc., serial number AGAR909E415822FA). The median (*Me*) with interquartile range (25 %; 75 %) – 25th and 75th percentiles ($Q1$ and $Q3$ – first and third quartiles, respectively) served as a central trend to describe quantitative traits with an abnormal distribution. Differences between groups were assessed by nonparametric Kruskal–Wallis H-test analysis of variance for means, for relative values by χ^2 criterion, including Yates's correction at values close to 0. To assess the relationship between traits, a correlation analysis was performed by calculating Spearman’s rank correlation coefficient (ρ). The critical value of the level of statistical significance (p) for all types of analysis was less than 5 % ($p<0.05$).

Results of the study and their discussion. Among the examined patients, women accounted for 128 (70.3 %), men were 54 (29.7 %), the ratio of women to men – 2.37:1. In patients with the generalized form of the disease, a statistically significantly higher proportion of men was determined, compared with the ocular form (p=0.027). However, statistically significant differences in the overall structure of the examined by sex were not found between classes and subclasses of the disease ($p>0.05$).

The age of all patients at the time of examination ranged from 18 to 83 years. The median age in the examined patients was 52.0 years with an interquartile range (34.0; 65.0).

Antibodies to AchR were detected in 124 (68.1 %) patients, including 108 (73.5 %) with generalized and 16 (45.7%) with ocular form of the disease.

The second marker in the frequency of detection were antibodies to MuSK, which was detected in 16 (10.9 %) patients with generalized myasthenia gravis. These antibodies were not detected in patients with ocular myasthenia gravis.

Antibodies to titin were detected in almost a third of all subjects – in 53 (29.1 %) people. These antibodies were not detected in patients with ocular myasthenia gravis.

Antibodies to SOX1 were also not detected in patients with ocular myasthenia gravis, but were diagnosed in 10 (6.8 %) subjects with generalized form.

When analyzing the intensity of the disease (Fig. 1) on the QMG scale (0-9 points – mild; 10-16 points – moderate; 17 points or more – severe degree), it was found that in all patients of Class I and the predominant proportion (90.4 %) of Class II were determined by a mild degree of the disease, while in patients of Class III and IV there was mostly moderate (87.5 % and 51.6%) degree of myasthenia gravis ($p<0.001$).

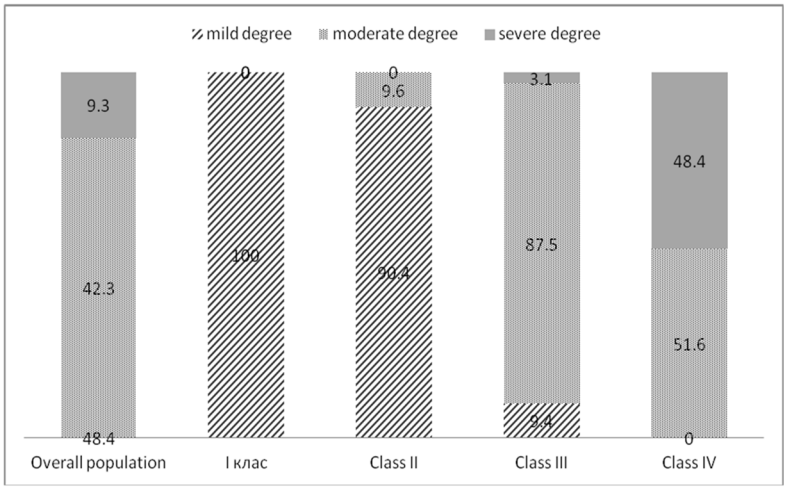

Fig. 1. Distribution of the examined patients by the degree of myasthenia gravis (according to QMG scale) depending on the class of disease (%).

Notes: differences between classes – *p<0.001* by the χ^2 criterion.

The mean level of SA in patients with ocular form was 44.0 (41.0; 48.0) points (median and interquartile range), which corresponds to a moderate level of SA and does not require correction. Mean SA level in patients with generalized myasthenia gravis was 53.0 (45.0; 59.0) points (*p<0.001*), which corresponds to a severe level of SA and requires its correction. The mean SA level in the general sample is 50.0 (44.0; 59.0), which corresponds to a high SA level.

The SA level in patients with different classes and subclasses of generalized myasthenia gravis was assessed separately by MGFA. The mean SA level in patients with Class II myasthenia gravis was 45.5 (45.0; 55.0), in subclass II-a – 45.0 (41.0; 54.0), in subclass II-B – 46.0 (45.0; 55.0). Indices between subclasses do not differ significantly ($p>0.05$). The level of SA in the group of patients with Class II myasthenia gravis slightly exceeds the level of moderate SA.

The mean SA level in patients with Class III myasthenia gravis was 51.5 (46.5; 59.0), in subclass III-a – 50.0 (43.0; 59.0), in subclass III-B – 43.0 (50.0; 59.0). Indexes between subclasses do not differ significantly ($p>0.05$). The level of SA in the group of patients with Class III myasthenia gravis corresponds to a severe level of SA.

The mean SA level in patients with Class IV myasthenia gravis was 64.0 (56.0; 70.0), in subclass IV-a – 64.0 (55.0; 70.0), in subclass IV-B – 65.0 (59.0; 73.0). Indexes between subclasses do not differ significantly ($p>0.05$). The level of SA in the group of patients with Class IV myasthenia gravis corresponds to a severe level of SA. SA values differ significantly between classes II-IV ($p<0.001$).

The distribution of patients according to the SA severity depending on the clinical form of myasthenia gravis was assessed separately (table 1).

Table 1

Distribution of patients with ocular and generalized myasthenia gravis depending on the level of state anxiety

Indices	Overall population n=182	Ocular form n=35	Generalized form n=147
Mild (up to 30 points), n (%)	4 (2.2)	1 (2.9)*	3 (2.0)*
Moderate (31-44 points), n (%)	133 (73.1)	17 (48.6)*	116 (78.9)*
Severe (≥45 points), n (%)	45 (24.7)	17 (48.6)*	28 (19.1)*

Notes. * – $p<0.05$. Differences between groups were assessed by nonparametric Kruskal–Wallis H-test analysis of variance for means, for relative values by χ^2 criterion, including Yates's correction at values close to 0.

As can be seen from table 1, mild SA levels are recorded in significantly more patients with ocular myasthenia gravis compared to generalized ones. In contrast, moderate SA is observed in a significantly larger number of patients with generalized myasthenia gravis. This indirectly confirms the fact that the degree of clinical manifestations can significantly affect the increase in SA.

For a more in-depth analysis of the obtained data, the distribution of patients with different classes and subclasses of generalized myasthenia gravis according to MGFA depending on the level of SA was studied separately (table 2).

Table 2

Distribution of patients with different classes of generalized myasthenia depending on the level of state anxiety

Indices	II–A n=37	II–B n=15	Class II n=52	III–A n=35	III–B n=29	Class III n=64	IV–A n=14	IV–B n=17	Class IV n=31
Mild (up to 30 points), n (%)	1 (2.7)	0 (0)	1 (1.9)*	2 (5.7)	0 (0)	2 (3.1)*	0 (0)	0 (0)	0 (0)*
Moderate (31-44 points), n (%)	17 (4.0)	3 (20.0)	20 (38.5)*	8 (22.9)	0 (0)	8 (12,5)*	0 (0)	0 (0)	0 (0)*
Severe (≥45 points), n (%)	19 (51.4)	12 (80.0)	31 (59.6)*	25 (71.4)	29 (100.0)	54 (84.4)*	14 (100.0)	17 (100.0)	31 (100.0)*

Notes. * – p<0.001. Differences between groups were assessed by nonparametric Kruskal–Wallis H-test analysis of variance for means, for relative values by χ^2 criterion, including Yates's correction at values close to 0.

As can be seen from table 2, the number of Class II and III patients with mild SA was insignificant, which somewhat complicates the clinical interpretation of the data. Significantly more patients with Class II and III myasthenia gravis had severe SA levels. At the same time, among patients with Class II, there was a significant proportion of patients with moderate SA levels, in contrast to patients with Class III myasthenia gravis, who had mostly severe SA levels. All patients with Class IV myasthenia gravis had severe SA levels.

Thus, the obtained data confirm the influence of the growth of clinical manifestations (and, consequently, the class of myasthenia gravis according to MGFA) on the increase of SA levels.

For a more in-depth analysis of factors potentially affecting the level of SA in patients with myasthenia gravis, some comparisons were made (using the Spearman rank correlation method). The levels of SA correlate with patients' age (p=0.19; p=0.008) and the clinical form of myasthenia gravis (p=-0.35; p=0.003). There was a significant correlation between the indices of the quantitative assessment of the severity of myasthenia gravis (on the QMG scale) and the results of the SA assessment (ρ=0.54; p<0.001*).* The data obtained confirm that the degree of clinical manifestations of the disease significantly affects the level of anxiety of patients in general.

The SA level correlates with the presence of (p=0.24; p<0.001) and the titer of antibodies to AchR (p=0.46; *p<0.001*). No correlations were found between SA levels and the presence, as well as with the antibody titer to MuSK (p=0.07; p=0.35 and ρ=0.09; p=0.28 accordingly), with the presence of antibodies to titin (p=0.13; p=0.08*),* with the presence of antibodies to SOX1 (p=0.13; p=0.08*)*.

When comparing the age of the first symptoms of the disease, the age of diagnosis and the time from the onset of the first symptoms to diagnosis with the assessment of SA, no significant correlations were found (p=0.12, p=0.12*;* ρ=0.13, p=0.09 and ρ=0.06; p=0.46 respectively). This confirms that neither the age of the patients nor the duration of the disease have a significant effect on the level of SA in contrast to the degree of clinical manifestations.

Thus, neuropsychological changes, in particular, increased anxiety, are one of the leading symptoms in the structure of comorbidity in patients with myasthenia gravis. According to Ybarra M. et al., 46.3 % of patients with myasthenia gravis have increased anxiety, and the frequency of registration of increased anxiety in myasthenia gravis corresponds to this frequency in other chronic diseases [15]. According to Alekseeva T.M. et al., moderate or severe depression is registered in 20.3 % of patients with myasthenia gravis, and increased anxiety – in 26.1 % of patients [4]. These data do not coincide with the results of our study, because the frequency of increased anxiety (in terms of SA) in myasthenia gravis was much higher, in addition, the structure of anxiety differed (dominated by moderate and severe levels of anxiety). Such results can be explained by different methods of assessing anxiety on the one hand, and different samples by the number of outpatients and inpatients, on the other.

According to our study, it is confirmed that the degree of clinical manifestations of myasthenia gravis is one of the main factors influencing the increase in anxiety in patients with myasthenia gravis in general. Similar results are given by other authors [6, 8, 11, 13, 15].

The data obtained as a result of our study prove the need for neuropsychological examination of patients with myasthenia gravis in order to personalize and optimize the treatment.

Conclusions

1. The level of SA was significantly higher in patients with generalized myasthenia than in patients with ocular myasthenia.

2. The increase in the degree of clinical manifestations of myasthenia gravis significantly leads to an increase in the level of SA. This fact should be taken into account when planning treatment tactics for each individual patient.

3. The age of patients and the duration of the disease in myasthenia gravis do not significantly affect the level of SA in patients.

4. The presence and titer of antibodies to AchR correlated with the level of SA.

Prospects for further research are that it is promising to study the impact of anxiety and depression on the quality of life of patients with myasthenia gravis, as well as to study and compare the structure of neuropsychological changes separately in outpatients and inpatients.

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