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IMMUNE RESPONSE OF ESCHERICHIOSIS INFECTED CHILDREN WITH EPSTEIN-BARR VIRUS

© Ye. Olkhovskyi

Досліджено показники імунної відповіді і фагоцитарної активності нейтрофілів при ешеріхіозі у дітей раннього віку, інфікованих вірусом Епштейна-Барр (ВЕБ). Доведено, що перебіг ешеріхіозу у дітей на тлі латентної форми ВЕБ-інфекції супроводжується пригніченням клітинної ланки імунної відповіді, активацією гуморального імунітету і ознаками напруження функціональної активності нейтрофілів
Ключові слова: *ешеріхіоз, вірус епштейна-барр, діти, клітинний і гуморальний імунітет, нейтрофіли*

1. Introduction

Escherichiosis takes the leading place among bacterial intestinal infections which is relevant especially among children of first year of life due to the threat of dehydration and severe complications [1, 2]. Bacteria and lipopolysaccharides of bacterial cell membranes are one of the triggering factors in the development of the inflammatory process in the body, the cause of which largely depends on the protective reaction of the organism, both specific and non-specific links. The non-specific factors of anti-inflammatory and antimicrobial response include the phagocytic activity of neutrophils and monocytes. Presently scientists use nitroblue tetrazolium reduction test (NBT-test) to study the bactericidal activity of neutrophils in many infectious and non-infectious diseases. Some data point to the prognostic value of the NBT-test and the possibility of its use as a recovery criterion for infectious pathology [3, 4].

2. Case presentation

In the case of human infection, the leading role belongs to the immune response which plays a major role in the recognition of an indefinitely large number of various antigen molecules and their subsequent destruction and elimination from the organism [5]. The study of subpopulations of lymphocytes makes it possible to characterize the state of the cellular link of the immune response, which is realized with the help of antigen-specific recognition receptors of lymphocytes [6, 7]. Many works are devoted to the investigation of subpopulations of serum lymphocytes in patients with bacterial intestinal infections, including Escherichiosis, but these results are often controversial and require further research [8, 9]. B-lymphocytes are extremely important in the production of antibodies of different specificity. In infectious diseases, IgM antibodies with low avidity appear first, which are soon replaced by IgG antibodies with high avidity. Antibodies of IgA class also belong to high-avidity ones, the secretory form of which plays an important role in maintaining local immunity. The timeliness and adequacy of antibody-formation is responsible for the complete recovery of a person from an infectious disease and is often a protective factor, this is why the study of immune response in intestinal infections is of utmost interest to many scientists and remains relevant [10, 11].

The condition and functional activity of the immune system of the child's organism can be affected by different factors, among which is the infection of children by herpes viruses, especially the Epstein-Barr virus (EBV) which occurs primarily during the first three years of life and may be accompanied by a virus infection of the lymphatic system and immune cells [7, 12]. The prolonged persistence of herpes group viruses in the human body can lead to "malfunctions" in the normal functioning of the immune system which does not exclude the impact on the course of the underlying disease, including Escherichiosis. But according to the sources available to us, we have not found any studies on the state of the immune response at Escherichiosis in children infected with EBV.

3. Aim of research

Study the features of the immune response in Escherichiosis of children infected with EBV to improve early diagnosis of infection with EBV and the therapy of these patients.

4. Materials and methods of research

During 2015–2017 on the basis of the Children's Regional Infectious Clinical Hospital in Kharkov, we examined 84 children aged from one to three years with Escherichiosis who were divided into three groups. The first group included 28 children with Escherichiosis against a background of persistent inactive (latent) EBV infection, the second – 26 patients with Escherichiosis on the background of active EBV infection. The third group consisted of 30 patients with Escherichiosis without concomitant infection with any viruses (mono-infection).

The diagnosis was made in accordance with ICD-10, taking into account the clinical, bacteriological, virological and serological studies of patients. Persistent non-active EBV infection was diagnosed when the patient had high titers of antibodies to the capsid antigen (EBV CA) of the IgG class in the dynamics of the disease (latent form). Active EBV infection was determined by detection of antibodies to the capsid antigen (EBV CA) of the IgM

class in the patient, the presence of EBV in the patient's secretions (saliva, blood) by PCR.

The condition for exclusion from the cohort of the study was detection in patient's markers of other herpes viruses (CMV, herpes virus type 6). Children of all groups were compared in ages (19.2±2.1, 23.6±3.4 and 20.4±1.6 months ($p>0.05$) and sex. In addition to the conventional methods of investigation, the levels of subpopulations of CD3, CD4, CD8, CD19, CD21 lymphocytes of peripheral blood were determined using monoclonal antibodies with a solid-phase enzyme immunoassay method ("Sorbent", Russian Federation); determination of phagocytic activity of peripheral blood neutrophils by NBT-test; determination of the state of the humoral part of the immune response by IgM, IgA, IgG content of blood serum using the immune enzyme method with standard sets "IFA-BEST" (Russian Federation). In the study of the phagocytic activity of neutrophils, the spontaneous NBT-test (NBTsp) and stimulated (NBSst) were determined, and the neutrophil activation index (spontaneous and stimulated) was calculated (IANsp and IANst). Investigation of the parameters of the cellular and humoral immune response, phagocytic activity of serum neutrophils of patients with Escherichiosis was carried out in acute period (1–2 days of illness) and in the period of early reconvalescence (7–10 days of illness).

The control group consisted of 20 practically healthy children, similar in age (21.5±2.8 mon.) and sex (their data were taken as reference values).

Static processing of the obtained results was carried out by means of Excel and Statistics 6.0 applications. Test of normality was carried out according to the criterion of Kolmogorov-Smirnov. The significance of differences between groups was determined using the t-test (Student's test).

5. Results of the research

In the acute period of Escherichiosis, in all patients there was a decrease in the number of CD3+, CD4+ and CD8+ lymphocytes in blood, this indicates a suppression of the cellular part of the immune response. The decrease in CD3+ lymphocyte content in mono-infected patients was not significant ($p>0.05$), while in the infected ones with EBV, the decrease was significant with maximum expression in the latent form of EBV infection ($p<0.05$ and $p<0.01$ respectively). The most significant reduction in the number of CD4+ lymphocytes is defined in patients with Escherichiosis and infected by EBV infection regardless of its activity ($p<0.001$). The CD19+ score, which is closely related to the humoral part of the immune response was significantly higher than the reference values in patients with Escherichiosis. The maximum increase in CD19+ was observed in patients with mono-infection ($p<0.001$) and this increase was significant compared to patients with Escherichiosis against the background of EBV infection, regardless of its activity ($p<0.05$). The significant increase in the content of CD21+ lymphocytes in patients with Escherichiosis was detected only in the presence of concomitant EBV infection with maximum severity in patients with active forms of EBV. Indicators in these patients significantly differed from those of patients with Escherichiosis on the background of the latent form of EBV ($p<0.05$) and from the indicators of children with mono-infection ($p<0.05$).

The study of the concentration of the main classes of serum immunoglobulines in patients with Escherichiosis did not reveal a significant difference in IgM between groups and in comparison with healthy children, although the tendency to increase this index was observed in all patients ($p>0.05$). Infection of EBV in patients with Escherichiosis leads to significant increase of blood IgG in comparison with control, while the most significant difference of the index was observed in patients with latent EBV infection ($p<0.01$). The blood IgG content in the patients of the first group significantly differed from the data of the children of the second ($p<0.05$) and the third group ($p<0.01$). In the acute period of Escherichiosis, we did not see any significant differences in the IgA content in the study groups, although all patients with Escherichiosis had an increase in IgA compared to healthy children ($p>0.05$).

Indicators of the main subpopulations of lymphocytes, the content of serum IgM, IgA, IgG and the results of the NST-test of patients in different periods of Escherichiosis are given in the Table 1.

The acute period of Escherichiosis is accompanied by a significant increase in the functional activity of neutrophils in children with a maximum increase in the NBTsp-test in patients with mono-infection ($p<0.01$). It was found that in the patients of the first group, the NBTsp-test was significantly lower than the data of the second and the third groups ($p<0.05$). The IANsp in the first group was elevated, but did not differ significantly from healthy children ($p>0.05$), while in patients of the second and third groups this indicator was significantly higher ($p<0.01$). The evaluation of the functional reserve of the oxygen-dependent bactericidal mechanism of neutrophils revealed minimal possibilities in patients with Escherichiosis on the background of latent EBV infection: the indices of the NBTst-test of these patients were lower and did not differ significantly from those of healthy children, ($p>0.05$). Significantly higher NBTst-test values were observed in patients with mono-infection and in Escherichiosis with active EBV infection: data of this group was differed compared to the healthy children, as well as to the patients of the first group ($p<0.05$ and $p<0.01$, respectively). The highest IANst values were determined in patients of the second and third groups ($p<0.01$).

The analysis of the dynamics of the studied parameters of patients in the period of early convalescence of Escherichiosis revealed the following (Table 1). In all patients, the increased levels of CD3+, CD4+ and CD8+ blood lymphocytes were observed in the recovery period of Escherichiosis ($p<0.01$), and in patients with mono-infection the content of these indicators exceeded the data of healthy children. At the same time, in patients with Escherichiosis on the background of EBV infection, these indices remained significantly lower compared to patients with mono-infection ($p<0.001$). There was no significant difference in levels of CD4+ and CD8+ lymphocytes between the first and second groups ($p>0.05$).

Table 1

Levels of subpopulations of lymphocytes, immunoglobulins and phagocytic activity of neutrophils, (Mean±SE)

Indexes	Period of illness	1 group (n=28)	2 group (n=26)	3 group (n=30)	Control group (n=20)
$CD3^+$, %	Acute	53.64±0.63; P<0.001; P_1<0.05; P_2<0.01	56.01±0.54; P<0.05; P_2<0.05	58.64±0.71; P>0.05	60.60±1.20
	Convalescence	55.34±0.47; P<0.001; P_1<0.01; P_2<0.001	58.12±0.34; P>0.05; P_2<0.001;	62.43±0.57; P>0.05;	
$CD4^+$, %	Acute	28.49±0.55; P<0.001; P_1>0.05; P_2<0.001	27.68±0.61; P<0.001; P_2<0.001	33.94±0.38; P<0.05	36.30±0.75
	Convalescence	31.06±0.43; P<0.001; P_1>0.05; P_2<0.001	30.24±0.52; P<0.001; P_2<0.001	39.94±0.26; P<0.001;	
$CD8^+$, %	Acute	18.32±0.41; P<0.001; P_1>0.05; P_2<0.001	17.38±0.72; P<0.001; P_2<0.001	23.28±0.31; P<0.05	25.70±0.68
	Convalescence	22.16±0.34; P<0.001; P_1>0.05; P_2<0.001	21.48±0.63; P<0.001; P_2<0.001;	27.24±0.61; P>0.05;	
CD 19^+, %	Acute	19.18±0.62; P>0.05; P_1<0.05; P_2<0.05	20.24±0.68; P<0.01; P_2<0.05	23.75±0.87; P<0.001	17.30±0.79
	Convalescence	21.52±0.24; P<0.001; P_1>0.05; P_2>0.05	20.87±0.47; P<0.01; P_2 >0.05	21.17±0.28; P<0.001;	
$CD21^+$, %	Acute	20.17±0.62; P<0.05; P_1<0.05; P_2 >0.05	23.54±0.84; P<0.001; P_2<0.05	17.44±1.56; P>0.05	17.03±1.27
	Convalescence	19.64±0.37; P<0.05; P_1<0.001; P_2 >0.05	21.84±0.45; P<0.01; P_2<0.05	17.29±0.83; P>0.05	
IgM, g/l	Acute	0.82±0.34; P>0.05; P_1>0.05; P_2 >0.05	0.88±0.21; P>0.05; P_2 >0.05	0.71±0.12; P>0.05	0.62±0.23
	Convalescence	1.38±0.26; P<0.05; P_1>0.05; P_2 >0.05	1.88±0.31; P<0.01; P_2<0.01	1.14±0.09; P>0.05;	
IgG, g/l	Acute	10.84±0.66; P<0.01; P_1<0.05; P_2<0.01	8.24±0.28; P<0.05; P_2 >0.05	7.48±0.37; P>0.05	7.22±0.27
	Convalescence	11.64±0.46; P<0.001; P_1>0.05; P_2<0.01	11.19±0.16; P<0.001; P_2<0.001	9.94±0.17; P<0.001;	
IgA, g/l	Acute	0.72±0.18; P>0.05; P_1>0.05; P_2 >0.05	0.79±0.17; P>0.05; P_2 >0.05	0.69±0.15; P>0.05	0.58±0.24
	Convalescence	1.21±0.18; P<0.05; P_1>0.05; P_2 >0.05	1.57±0.25; P<0.01; P_2<0.05	0.81±0.10; P>0.05;	
NCTsp,%	Acute	13.54±0.57; P<0.05; P1<0.05; P2<0.05	17.15±1.38; P<0.05 ; P2>0.05	20.57±2.99; P<0.05	9.34±1.45
	Convalescence	11.07±0.42; P>0.05; P1<0.05; P2 >0.05	12.48±0.48; P>0.05; P2 >0.05	11.24±1.54; P>0.05;	
IANsp, ум.од.	Acute	0.20±0.08; P>0.05; P1>0.05; P2>0.05	0.27±0.03; P<0.01; P2 >0.05	0.33±0.05; P<0.05	0.13±0.01
	Convalescence	0.17±0.06; P>0.05; P1>0.05; P2 >0.05	0.19±0.04; P>0.05; P2 >0.05	0.23±0.09; P>0.05;	
NCTst, %	Acute	37.22±0.57; P>0.05; P_1<0.05; P_2<0.01	52.59±2.41; P<0.05; P_2 >0.05	51.86±2.97; P<0.05	40.05±2.16
	Convalescence	38.09±0.31; P>0.05; P_1<0.001; P_2<0.01	45.18±1.27; P>0.05; P_2 >0.05	43.29±1.68; P>0.05;	
IANst, ум.од.	Acute	0.67±0.04; P<0.05; P_1>0.05; P_2<0.05	0.82±0.03; P<0.01; P_2 >0.05	0.93±0.09; P<0.01	0.51±0.06
	Convalescence	0.53±0.04; P>0.05; P_1>0.05; P_2 >0.05	0.56±0. 08; P>0.05; P_2 >0.05	0.48±0.07; P>0.05;	

Note: P – reliability of a sign to the control group; P_1 – reliability of a sign between the first and second groups; P_2 – reliability of a sign to the third group

The course of Escherichiosis in children infected with EBV is accompanied by a significant inhibition of the cellular link of the immune response, which is maximally expressed in latent form of EBV infection ($p<0.001$). Multidirectional changes in the CD19+ lymphocyte count have been revealed: in patients with mono-infection, the levels of CD19+ lymphocytes raised in the acute period decreased; in the presence of EBV infection - this indicator tended to increase, significantly differing from those of healthy children ($p<0.001$). In the period of convalescence in children infected with EBV, a high content of CD21+ lymphocytes is maintained with the maximum increase on the background of active EBV infection ($p<0.01$). Serum immunoglobulin levels in the patients of the observation groups in the period of convalescence were increased. Concentration of IgM was significantly higher in patients of the second group ($p<0.01$); in the first and third groups this increase was less significant compared to healthy children ($p<0.05$). IgG levels in patients in all groups were significantly different from those of healthy children ($p<0.001$). Regardless of the activity of EBV infection ($p>0.05$), IgG levels in patients infected with EBV was significantly higher compared with patients with mono-infection ($p<0.01$). Concentration of IgA in blood in the period of convalescence of Escherichiosis in children with active EBV infection was significantly higher than in patients with mono-infection ($p<0.05$) and in healthy children ($p<0.01$). There was no dependence of IgA levels on activity of EBV infection in patients with Escherichiosis ($p> 0.05$). The content of IgA was not significantly increased in children with mono-infection (3 group), ($p>0.05$).

In the period of convalescence of Escherichiosis, a significant decrease the indicators of functional activity of neutrophils was determined, which were close to the indices of healthy children, ($p>0.05$). In patients infected with EBV, difference in the NBTsp-test was found, which depended on the activity of the process: in patients with active EBV infection, this indicator remained significantly higher ($p<0.05$). The IANsp was significantly reduced in all patients in the period of convalescence of Escherichiosis and did not differ from those of healthy children ($p>0.05$). The metabolic potential of phagocytes in patients in the recovery period of Escherichiosis was considerably improved: NBTst indices in all groups did not differ significantly from the data of healthy children ($p>0.05$). But, the attention was drawn to the multidirectional dynamics of NBTst-test in patients. Thus, in case of mono-infection and Escherichiosis with active EBV infection, the decrease of this indicator in the dynamics of the disease was determined ($p<0.05$). In patients with Escherichiosis and latent EBV infection, insignificant fluctuations (increase) in NBTst-test ($p>0.05$) were observed, which reliably differed from the results of patients of the second and third groups ($p<0.05$). The IANst in the period of reconvalescence was significantly reduced in all patients ($p<0.05$); while remaining elevated, it did not differ significantly from the reference values ($p>0.05$).

6. Discussion

The analysis of the immune response in acute period of Escherichiosis in children with latent EBV infection revealed significant inhibition of the cellular link of the immune response; activation of humoral immunity (high IgG level); reliable increase in the functional activity of neutrophils (but less pronounced in comparison with mono-infection and Escherichiosis in children with active EBV infection); decrease in the functional reserve of the oxygen-dependent mechanism of bactericidal neutrophils. The course of Escherichiosis in young children with active EBV infection is accompanied by similar changes in the immune response (as in patients of the first group), but with a significant activation of oxygen-dependent neutrophils metabolism without signs of reduction in its adaptive capacity. The immune response of patients in the acute period of Escherichiosis (mono-infection) is characterized by insignificant changes in the content of CD3+ and CD21+ -cells, a decrease in CD4+ and CD8+ with a significant increase in CD19+ lymphocytes; indicators of the humoral link of the immune response remain without significant dynamics. For these patients, the increased functional activity of neutrophils with a high functional reserve of bactericidal neutrophils was typical. The significant decrease in T-lymphocytes (helper and cytotoxic) detected by us in the group of infected EBV children in the acute period of Escherichiosis does not contradict the results of other authors pointing to the immunosuppressive effect of EBV on the lymphocyte cell pool [7, 13]. According to the results of some authors, an increase in CD8+- lymphocyte levels was noted against the background of low CD4+-lymphocyte parameters, but these studies concerned infectious mononucleosis as mono-infection [14]. In our opinion, the increase in the levels of immunoglobulins in Escherichiosis in patients infected with EBV is explained by the activation of compensatory mechanisms of the humoral part of the immune response, whose role is undoubted in intestinal infections [15]. These changes do not contradict the revealed increase in the level of CD19+-lymphocytes. Escherichiosis in children with latent EBV infection is accompanied by less significant activation of functional activity of phagocytes with a decrease in the functional reserve of the oxygen-dependent mechanism of bactericidal neutrophils. Other researchers are indicating a violation of the functional reserve of neutrophils, but these studies were performed in patients with mono-bacterial or mono-viral infections [3, 16]. Unfortunately, in the sources available to us there are no works that would be related to the phagocytic activity of neutrophils in viral-bacterial mixed-infections, in particular in case of Escherichiosis in children infected by EBV.

In the period of convalescence of Escherichiosis in patients infected with EBV, there was no complete recovery of the cellular link of the immune response, the state of immunosuppression was maintained, which was maximally expressed in children with latent form of EBV infection ($p <0.001$). In the presence of EBV infection in children with Escherichiosis, there was a tendency to increase the levels of CD19+ lymphocytes with a signifi-

cant difference from the reference values ($p < 0.001$). The course of Escherichiosis in patients infected with EBV was characterized by a high concentration of CD21+ lymphocytes, with the most pronounced changes in the active form of EBV infection ($p < 0.01$). Levels of all classes of immunoglobulines were kept elevated in patients of all groups. The maximum increase in IgM, IgG and IgA content was determined in patients with Escherichiosis and EBV infection. Based on the index of NBTsp-test in patients with Escherichiosis and active EBV infection, the tension of functional activity of phagocytes compared with patients with Escherichiosis and latent form of EBV infection were revealed ($p<0.05$). Estimation of the functional reserve of the oxygen-dependent mechanism of bactericidality of neutrophils discovered minimal opportunities in patients with Escherichiosis on the background of latent EBV infection: the NBTst-test data of these patients were reduced and significantly differed from those of patients in the second and third groups ($p<0.05$).

Thus, the obtained data of indices of specific and non-specific protective response of children with Escherichiosis infected with EBV, made it possible to reveal various pathogenetic mechanisms of the development of an infectious disease depending on the background infection. But, we understand that in order to more complete study the main pathogenetic mechanisms, it is necessary to continue investigating other parameters of the immune response.

7. Conclusions

1. The course of Escherichiosis in children and immune response of patients depends on the background infection.

2. The presence of latent or active EBV infection in a child with Escherichiosis leads to inhibition of cellular immunity and tension of the humoral part of the immune response, over-strain of functional activity of neutrophils, and at case of latent form of EBV infection – decreasing of the functional reserve of the oxygen-dependent mechanism of bactericidal neutrophils in acute period of Escherichiosis.

3. In the early recovery period of Escherichiosis, there is no complete restoration of the parameters of specific and non-specific immune response in children infected with EBV, which creates conditions for a wave-like course of the main disease, increases the risk of contamination by any other infection.

4. In our opinion, the obtained data should be taken into account in terms of medical observation of patient with Escherichiosis in recovery stage depending on the background infection, as well as for adequate treatment of these patients.

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Olkhovskyi Yevhen, Postgraduate student, Department of children infectious diseases, Kharkiv national medical university, Nauky ave., 4, Kharkiv, Ukraine, 61022
E-mail: olkhov91@gmail.com

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ОЦІНКА ЯКОСТІ ЖИТТЯ У ХВОРИХ НА МІАСТЕНІЮ

© О. І. Кальбус

У статті представлено результати дослідження якості життя у 96 хворих на міастенію в залежності від імунологічного типу, тривалості та клінічної форми захворювання. Розвиток тривожних порушень у хворих на міастенію збільшується з тривалістю перебігу хвороби, залежить від тяжкості міастенії, не залежить від імунологічного типу захворювання. Тривожні прояви більш виражені у хворих на генералізовану міастенію

Ключові слова: *міастенія, якість життя, антитіла до рецепторів ацетилхоліну, антитіла до м'язово-специфічної тирозин-кінази*

1. Вступ

Міастенія є актуальною проблемою неврології через зростаючу захворюваність [1] та поширеність [2] з одного боку, а також через потенційну курабельність пацієнтів – з іншого [3].

За даними різних авторів, захворюваність на міастенію складає від 1,7 до 10,4 випадків населення в рік, а в США досягають до 20 випадків на 100 тисяч населення у рік [3, 4]. Поширеність захворювання протягом останнього десятиліття зростає, головним чином у літніх людей, незважаючи на значний прогрес у діагностиці, лікувальних підходах та покращенні прогнозу захворювання в цілому [4, 5].

Враховуючи хронічний характер захворювання, у хворих на міастенію можуть розвиватися психологічні та психічні порушення, в тому числі депресія та підвищена тривожність, які можуть впливати на якість життя хворих з одного боку, та бути предиктором «псевдо-декомпенсації» хворих з іншого [6, 7]. Якість життя хворих на міастенію на даний час в Україні вивчена недостатньо та потребує подальшого вивчення з метою оптимізації лікувальних підходів та підвищення соціальної активності.

2. Обґрунтування дослідження

Запропоновані раніше підходи до діагностики міастенії включали клінічне обстеження, проведення прозеринової проби, використання електронейроміографії [3, 4]. Окрім цих методів на даний час доцільно проводити імунологічне обстеження з визначенням антитіл до рецепторів ацетилхоліну та/або м'язово-специфічної тирозин-кінази з визначенням імунологічного підтипу захворювання з метою підбору оптимальної лікувальної тактики [1, 3].

Етіологія міастенії на даний час не встановлена, втім доведена аутоімунна природа захворювання [2]. Втрата (блокування) близько 60 % рецепторів ацетилхоліну призводить до розвитку м`язової слабкості – основного клінічного прояву міастенії [3].

За даними закордонної літератури, приблизно у 80–85 % пацієнтів з генералізованою і у близько 50 % хворих очної форм міастенії виявляються антитіла до рецепторів ацетилхоліну [1, 3]. Серед «серонегативних» пацієнтів можна визначити тих, що мають антитіла до м'язово-специфічної тирозин-кінази [4, 5].

Враховуючи хронічний характер захворювання, у хворих на міастенію погіршується якість життя, що призводить до соціальної дезадаптації [8, 9], погіршує прогноз перебігу захворювання в цілому [10]. Незважаючи на це, особливості змін якості життя у хворих на міастенію в Україні вивчені недостатньо та потребують подальшого уточнення з метою оптимізації лікувальної тактики та покращення психологічного, соматичного та соціального тсатусу хворих.

3. Мета роботи

Вивчення якості життя у дорослих хворих на міастенію в залежності від імунологічного підтипу та клінічної форми захворювання для оптимізації лікувальної тактики.