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CYTOKINE DISBALANCE AT HERPESVIRUS MYOCARDITIS

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Viral myocarditis is a heterogeneous group of diseases not only by etiologic factors, which belong to different families of Vira kingdom, but is also characterized by a unique mechanism of inflammatory process and cytokine levels specific for each of them [1]. According to numerous researches in cardio-immunology, at herpesvirus infection of the cardiovascular system occur both systemic and localized violations of the immune response [2, 3]. Every new research in this area approaches to understanding difficult immunopathologic processes that take place in a patient's organism, and enables to define the grounded directions of their correction. Cardiomyocytes inflammation itself causes about 10 % cases of cardiac insufficiency and after different authors, over 50 % of dilated cardiomyopathy [4, 5]. However, it is practically impossible to estimate data about actual disease incidence of viral myocarditis due to masked or asymptomatic clinical course in significant amount of cases. According to results of pathologoanatomic researches, frequency of this disease ranges from 0,12 to 12 %, that in its turn determines relevance of timely laboratory diagnostics of viral myocarditis [2, 6].

With appearance and application of molecular-biological methods of diagnostics into clinical practice, authentication of viral genomic fragments became possible, which appeared to confirm the hypothesis about the value of virus persistence in chronic or subacute myocarditis [7, 8]. Pathognomic, generally accepted diagnostic criteria of myocarditis, do not exist. For today, it is necessary to correlate clinical and laboratory criteria which represent inflammatory process in myocardium in order to confirm the diagnosis [9, 10].

Ubiquitousness and pantropism of Herpesviridae determines their direct participation in aetiopathogenesis, clinical implications, relapse and consequences of herpesvirus pathology of the cardiovascular system. Herpesvirus infection can damage all without exception heart membranes, causing the development of endocarditis, myocarditis, pericarditis and productive vasculitis of heart vessels, remaining not diagnosed [11].

The unique biological properties of all herpesviruses are their ability to escape factors of immune defence due to the protein synthesis which blocks the HLA receptors, causing violation of signals transmission to proliferation and differentiation in all the system of immune response, decline of interferon production, oppression of the activity of cytotoxic T lymphocytes with CD8 phenotype and other immunocompetent cells [12, 13]. Thus, transformation of acute herpesvirus infection into a chronic process takes place at the «forced consent» of the immune system and usually without clear clinical implications at the beginning of the disease. For this reason, the problem of the immune system reconstruction and, in particular, mechanisms of this reconstruction, and also features of the immune system functioning in herpesvirus myocarditis need the detailed study. Timely determination of the degree of immunological disbalance in its turn will contribute to the increase of efficiency of subacute and chronic forms of myocarditis diagnostics and will enable to prevent the development of heart cavities dilatation and decline in retractive ability of myocardium, which result in cardiac insufficiency. Unfortunately, the accessible literature did not provide the data analysis of complex cardio-immunological research that would take into account the features of herpesvirus myocarditis clinical course.

Thus, all mentioned above grounds relevance of immunodiagnosis directed on the exposure of dysimmunities by study of indices of general and local immunity with the estimation of the immune status in patients depending on the stage of exasperation or relapse of chronic herpetic infection in the complex of diagnostic tests [14, 15].

The purpose of our research was to determine features of the state of the immune system with the complex analysis of cytokine profile data, immune and interferon statuses in subacute and chronic forms of herpesvirus myocarditis.

Materials and methods. 87 myocarditis patients with the laboratory confirmed herpesvirus infection, who were receiving inpatient treatment in medical establishments of Kharkiv aged 19 to 47 years, among them 49 (56,3 %) – men and 38 (43,7 %) – women were examined. The average age was (M ± m) 36 ± 3,46 years old. The diagnosis of myocarditis was established according to the order № 436 by the Ministry of Healthcare of Ukraine from 03.07.2006 of clinical findings protocol.

In accordance with the term of myocarditis clinical course, the patients were divided in two sub-groups: 44 patients with subacute (from 2 to 6 months), and 43 patients with chronic (over 6 months) clinical course of viral myocarditis, including chronically relapsing or initially chronic myocarditis. The criteria of exception were: clinical implications of ischemic heart disease, symptomatic arterial hyperpiesis, congenital or acquired heart diseases and taking immunomodulating medicine.

The control group consisted of 40 practically healthy persons, without implications of cardial pathology, which correlated with patients of basic group by age and gender.

Definition of cytokine concentration: IL-2, IL-4, IL-6, IL-10, INF-γ, TNF-α in blood serum was conducted by the sets of reagents by CJSC «Vector-Best» (Novosibirsk) by the method of solid-phase enzyme-linked immunosorbent assay with the use of spectrophotometer Stat Fax 303 Plus. Population structure of lymphocytes with different antigenic determinants ($CD3^+$, $CD4^+$, $CD8^+$, CD16/56, $CD19^+$, $CD95^+$) was determined by monoclonal antibodies by cytofluorimetric assay with the use of flow cytometry system Beckman Coulter FC 500 (USA) in accordance with the given

instructions. Echocardiographic examination of patients was conducted using Imagic-5000 (Kontron Medical, France).

Obtained data processing was conducted with the use of parametric and non-parametric methods of biostatistics by programs EXEL-2003® and Biostatistics 4.03. The critical level of statistical significance was accepted p = 0,05.

Results According to data of instrumental examination, the patients of both sub-groups had different degrees of cardiac insufficiency implications, which is evidenced by the megascopic sizes of heart cavities: left ventricular end-systolic dimension (LV ESD) and left ventricular end-systolic volume (LV ESV), left ventricular end-diastolic dimension (LV EDD) and left ventricular end-diastolic volume (LV EDV), right atrium, right ventricle and left atrium (RA, RV, LA). The degree of intensity of these changes was higher in the group of patients with chronic clinical course of herpesvirus myocarditis. So, the level of ejection fraction (EF) in this group reached only 55,4 % of the level of the control group, while in subacute it was 22,6 % lower from the echocardiographic indices of the control group. The detailed description of the changes of echocardiographic examination involved in the research is shown in Table 1.

Table1. Indices of central hemodynamics in patients with herpesvirus infectious myocarditis (according to echo data)

Index	Patients with herpesvirus infectious myocarditis		Control group (n=40)
	Subacute (n=44)	Chronic (n=43)	
LV EDD (cm)	5,1 ± 0,1	6,6±0,15*	4,9±0,14
LV ESD (cm)	3,2±0,12	5,6±0,15*	3,1±0,11
LV EDV (ml)	124,0±6,47*	233,2±10,25*,**	114,1±5,65
LV ESV (ml)	50,4±4,04	152,6±10,16	46,7±3,28
EF (%)	49,6±1,7*	35,5±1,33*,**	64,1±1,2
RA (cm)	2,8±0,13	4,2±0,27	2,4±0,02
RV (cm)	2,5±0,06	3,5±0,19*	2,4±0,05
LA (cm)	3,1±0,13	4,7±0,36*	3,1±0,05

Note: *- authenticity of divergences between indices in sub-groups of the sick and control groups **- authenticity of divergences between the indices of patients with different forms of herpesvirus myocarditis clinical course.

The decline of retractive ability of myocardium it not only an exceptional result of inflammatory process of cardiomyocyte but is also the consequence of cascade immunological changes which are the result of protracted viral persistence [16]. It is precisely herpesvirus persistence that has a determining influence on the character of clinical course of myocardial inflammatory process, causing progression of the disease due to forming inadequate immune answer that makes impossible the elimination of virus out of cardiomyocytes as it takes place at myocarditis, caused by representatives of other families of viruses [17, 18].

The course of inflammatory process with providing intercellular co-operation of activated immunocytes is regulated by a complicated system of so-called cytokines – inflammation neuromediators of albuminous nature. Today over 200 cytokines are already known and every year their amount is increasing. It is common that the character of immune answer at myocarditis is determined by balance of the T-helpers of the 1-st and 2-nd types (Th1, Th2). IL-2, IL-6, TNF-α, INF belong to Th1 producers. The indicated cytokines activate macrophages, NK-cells, maturation of cytotoxic T-lymphocytes-killers, providing the development of cellular immune answer mainly, including at an intracellular infection which is herpesvirus infection.

Instead, IL-4 та IL-10, that are accountable for the development of humoral response, including production of IgE, are producted by Th2. In addition, IL-10 is an inhibitor in relation to Th1. Therefore, it seems grounded to estimate Th1 functional activity of the production of most meaningful regulatory pro-inflammatory cytokines: TNF-α, INF and IL-2, IL-6, and Th2 – of the production of IL-10 or IL-4.

The levels of pro- and anti-inflammatory cytokines in patients with herpesvirus myocarditis were analysed. The data obtained indicates the disbalance in their system, which above all is characterized by a considerable level increase of pro-inflammatory IL-6 up to 134,09 ± 22,72 pg/ml (control level 11,83 ± 1,64 pg/ml) and in relation to moderate growth of levels of IL-2 та TNF-α at subacute myocarditis (Table 2).

Table 2. Characteristic of cytokine status in patients with herpesvirus infectious myocarditis

Index, pg/ml	Patients with herpesvirus infectious myocarditis		Control group (n=40)
	Subacute (n=44)	Chronic (n=43)	
TNF-α	78,46 ± 8,21*, **	68,14 ± 6,81*	40,62 ± 6,23
INF-γ	48,20 ± 3,75*, **	57,14 ± 4,37	59,22 ± 9,46
IL-2	72,33±6,81*, **	51,68±9,54*	30,02 ± 0,84
IL-4	51,86 ± 9,22*	91,76 ± 12,75*, **	31,46 ± 2,52
IL-6	134,09 ± 22.72*, **	98,21 ± 27,64*	11,83 ± 1,64
IL-10	7,26 ± 1,02*	10,94 ± 0,23*, **	3,58 ± 0,11

Note: *- authenticity of divergences between indices in sub-groups of the sick and control groups **- authenticity of divergences between the indices of patients with different forms of herpesvirus myocarditis clinical course

Such increase in level of IL-6, in our opinion, is explained by action dualism of this interleukine, which pro-inflammatory effect on the final stage of inflammation course changes to anti-inflammatory. As a result, in a complex with IL-10 it limits the secretion of TNF-α. For this reason, its level remains high at chronic herpesvirus myocarditis and exceeds the level of the control group by over 8 times. In addition, there is an increase of levels of anti-inflammatory IL-4, IL-10 cytokines at the chronic form of herpesvirus myocarditis course by 2,9 and 3,1 times respectively. At the same time, the level of IL-10 increased not only in comparison with the level of the control group but also almost 2 times exceeded the proper index at subacute myocarditis.

Some researchers believe that high level of TNF-α plays an important role in the progress of myocarditis due to the cytopathic effect on cardiomyocytes, especially in combination with interferon. It is known that INF-γ limits viral shedding on undamaged cardiomyocytes due to blocking their ribosomal synthesis. However, among the patients with evolving course of herpesvirus myocarditis the dynamics of interferon level changes had certain features. INF-γ is a pro-inflammatory interleukine, and thus it was expected to have higher level at subacute myocarditis in comparison with chronic. Instead, its decline was discovered; in patients with subacute course the index value was the lowest. In our opinion, this phenomenon can be related to serious course of disease. All the examined patients had different degrees of cardiac insufficiency. At serious forms of course, formation of cardiac insufficiency can be mainly observed together with the increase of TNF-α levels and to a lesser extent of INF-γ, that can be the result of mast cells activity and in its turn to influence the synthesis of collogen and processes of myocardium remodeling.

According to the result of our researches in the three examined groups, the level of the given cytokine was the highest in the group of patients with chronic myocarditis. It accords with the promulgated data that evidences to interferon accumulation in the area of inflammation at acute myocarditis with its subsequent release into bloodstream at the change of inflammation to cardiosclerosis in the conditions of advance and chronization of infectious myocarditis.

According to numerous studies, during the acute stage of viral myocarditis the reactions of cellular component of immune system become activated, which is accompanied by production of pro-inflammatory cytokines [9]. In case of infectious herpesvirus myocarditis, rapid elimination of virus does not occur.

It is connected with lymphotrophy of this virus family and the development of virus-challenged immunosuppressive state that result in a more protracted term of stay of viral particles both in blood and in cardiomyocytes. In its turn, this feature is a pre-condition of formation of chronic infectious myocarditis with classic clinicopathologic constituents of inflammation signs in myocardium and formation of the secondary metainfective immunodeficiency.

It is confirmed by the data got from the patients whose term of disease exceeded 2 months. The dynamics analysis of pro-inflammatory and anti-inflammatory cytokines levels at subacute and chronic herpesvirus myocarditis testifies to transformation of the immune answer into a humoral type as evidenced in the obtained data of population and sub-population composition structure of lymphocytes (Table 3).

Table 3. Characteristic of membrane phenotype of lymphocytes in blood of patients with herpesvirus infectious myocarditis

Sub-populations of lymphocytes, %	Patients with herpesvirus infectious myocarditis		Control group (n=40)
	Subacute (n=44)	Chronic (n=43)	
CD3+	73,3 ± 1,42	70,9 ± 2,73	70,6 ± 1,76
CD3+CD4+	44,2 ± 1,46	40,4 ± 3,16	40,8 ± 2,31

CD3+CD8+	26,3 ± 1,38	26,8 ± 2,57	27,9 ± 2,98
CD3-CD16/56	11,7 ± 1,16*	14,1 ± 1,84	16,2 ± 1,91
CD3+CD16/56	4,9 ± 0,67*, **	6,2 ± 1,18*	13,8 ± 2,96
CD19+	12,1 ± 1,31	12,6 ± 1,42*	9,7 ± 0,59
CD3+CD25+	6,8 ± 1,20*,**	2,5 ± 0,43	3,2 ± 0,29
CD3+CD95+	26,0 ± 4,47*, **	21,0 ± 3,12*	7,8 ± 1,43

Note: *- authenticity of divergences between indices in sub-groups of the sick and control groups **- authenticity of divergences between the indices of patients with different forms of herpesvirus myocarditis clinical course.

Analysis of indices of T-cell helpers with phenotype CD3+CD4+ and cytotoxic T lymphocytes with phenotype CD3+CD8+ discovered the increase of CD3+CD4+ level in the sub-group of patients with subacute course of herpesvirus myocarditis. This circumstance testifies to stimulation of the immune system in reply to a viral antigen and confirms the development of hyper reactive syndromes. However, changes level of the indicated sub-populations of lymphocytes is not reliable, and that is why cannot be examined as diagnostically meaningful.

Instead, sub-population composition of natural killers underwent greater changes. On the basis of the confirmed herpesvirus etiology of the examined patients, an increase in the level of NK-lymphocytes with phenotype CD3-CD16/56 and TNK-lymphocytes with phenotype CD3+CD16/56 in both groups of patients with myocarditis would have been expected. Nevertheless, the decline in levels of the indicated sub-populations of lymphocytes in peripheral blood was discovered. At the same time, the level of these changes was reliable in the group of patients with subacute course of herpesvirus myocarditis, while in the chronic group it had a tendency character. The discovered feature of immunological disbalance testifies not only to a certain degree of immunodeficient state but also to the development of autoimmune process. In this case, immunodepressive syndrome, which is accompanied by a system autoimmune reaction, can be examined not only as a factor of assistance of viral persistence but also as a factor of risk of inflammation progress and formation of cardiac insufficiency.

As the result of the conducted research, the increase in number of CD3+CD95+ lymphocytes of peripheral blood at myocarditis was discovered, especially in the group of patients with subacute herpesvirus myocarditis with its level exceeding the index of the control group by 3,3 times, and at chronic course – by 2,7 times. We consider that determination of CD95+ expression already has a prognostic value during the first signs of cardiac insufficiency. An increase in level of the indicated receptor is the evidence of active rejection process of defective and infected cardiomyocytes, which clinical displays are signs of cardiac insufficiency and decline of myocardium retractive ability.

Conclusion. Thus, determination of cytokine in blood serum at infectious myocarditis of herpesvirus nature has a high diagnostic value and can compete with invasion and instrumental methods of diagnostics. Disbalance in the system of cytokines at herpesvirus myocarditis is a universal reaction of the immune system which is characterized by the increased levels of pro-inflammatory cytokines against the moderate decline of anti-inflammatory, and the increase in concentration of IL-10 in combination with the level of lymphocytes of membrane phenotype CD3+CD95+ can be used as a diagnostic criterion of chronization course of disease.

Understanding the pathogenesis of viral myocarditis at cellular level matters for the development and optimization of methods of laboratory diagnostics and forms a basis for determining prognosis of a disease course and choice of treatment tactic.

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enzyme-linked immunosorbent assay, population structure of lymphocytes with different antigenic determinants ($CD3^+$, $CD4^+$, $CD8^+$, CD16/56, $CD19^+$, $CD95^+$) was determined by monoclonal antibodies by cytofluorimetric assay. Obtained data processing was conducted with the use of parametric and non-parametric methods of biostatistics by programs EXEL-2003® and Biostatistics 4.03. **Results and discussion.** The data obtained indicates the disbalance in their system, which above all is characterized by a considerable level increase of pro-inflammatory IL-6 up to 134,09 ± 22,72 pg/ml (control level 11,83 ± 1,64 pg/ml) and in relation to moderate growth of levels of IL-2 та TNF-α at subacute myocarditis. Such increase in level of IL-6 can take place due to the change of pro-inflammatory effect to anti-inflammatory in a remote period. In a complex with IL-10 IL-6 limits the secretion of TNF-α. For this reason, its level remains high at chronic herpesvirus myocarditis and exceeds the level of the control group by over 8 times. In addition, there is an increase of levels of anti-inflammatory IL-4, IL-10 cytokines at the chronic form of herpesvirus myocarditis course by 2,9 and 3,1 times respectively. At the same time, the level of IL-10 increased not only in comparison with the level of the control group but also almost 2 times exceeded the proper index at subacute myocarditis. Instead of the predicted INF-γ level rise, its decline was discovered, in patients with subacute course the index value was the lowest. This phenomenon can be the result of mast cells activity and in its turn influences the synthesis of collogen and processes of myocardium remodeling. Analysis of sub-population composition of lymphocytes discovered the increase in number of CD3+CD95+ lymphocytes of peripheral blood at myocarditis, especially in the group of patients with subacute herpesvirus myocarditis with its level exceeding the index of the control group by 3,3 times, and at chronic course – by 2,7 times. We consider that determination of CD95+ expression already has a prognostic value during the first signs of cardiac insufficiency. An increase in level of the indicated receptor is the evidence of active rejection process of defective and infected cardiomyocytes, which clinical displays are signs of cardiac insufficiency and decline of myocardium retractive ability. **Conclusion.** Thus, determination of cytokine in blood serum at infectious myocarditis of herpesvirus nature has a high diagnostic value and can compete with invasion and instrumental methods of diagnostics. Disbalance in the system of cytokines at herpesvirus myocarditis is a universal reaction of the immune system which is characterized by the increased levels of pro-inflammatory cytokines against the moderate decline of anti-inflammatory, and the increase in concentration of IL-10 in combination with the level of lymphocytes of membrane phenotype CD3+CD95+ can be used as a diagnostic criterion of chronization course of disease. Understanding the pathogenesis of viral myocarditis at cellular level matters for the development and optimization of methods of laboratory diagnostics and forms a basis for determining prognosis of a disease course and choice of treatment tactic.

Key words: herpesvirus myocarditis, immunological disbalance.

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