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IMMUNOLOGICAL DISBALANCE AT PATIENTS WITH ACUTE CORONARY SYNDROME IN THE CONDITIONS OF HERPETIC PERSISTENTION

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Cardiovascular diseases are the most widespread deceases in the structure of sick and death rate in Ukraine. Unfortunately, Ukraine could be referred to the countries where the following abnormality is responsible for the death of more than 50% of population. According to the epidemiology rates, the main reason of death is the coronary heart disease (CHD) and the acute coronary syndrome [1] as its consequence. For instance, while in GB the death rate of CHD declined by 42% amongst the men younger than 65 years old and by 49% amongst women of the same age accordingly, in Ukraine this rate raised by 19 % in the both groups within the period of 1994 -2004.

Currently in the capacity of indispensable part of pathogenesis of acute coronary syndrome the intravascular dolor is being under the consideration, destabilization of endothelium and herpes virus as the trigger factors of this process [2, 3] as well. Multicentre researches (SOLVD, VEST) showed the close connection between the raising level of proinflammatory cytokines and the severity of the CHD clinical course. When starting of virus reproduction in the endothelium cells quite fast infiltration by the polymorph nuclear cells, lymphocyte and macrophages with the lymphokine's secretion is observed, this eventually should lead to limitation of the cells being infected or to the virus reproduction inhibition [4, 5]. According to the modern presentation, the immune phlogistic activation is not only the cell

marker of the destabilization clinical course of atherosclerosis process, but also the independent factor of the high cardiovascular risks. However, the question of the virus induced immunological disbalance influence on the measurements of Cardio circulatory dynamics indexes, clinical course and after-effects of the ACS is still being poorly studied.

In connection with that, the purpose of our work is to define the distinctions of the immunology disbalance of the patients with acute coronary syndrome in the conditions of the long-lasting herpes virus persistent infection.

Materials and methods. Totally 20 patients were being examined (18 men and 2 women) for the acute coronary syndrome (ACS) who were under the treatment at the cardio department №2 clinic hospital №8 of the Kharkov city. The average age of the patients was ($53,9 \pm 2,8$) years old. Diacrisis of CHD and the form of its clinical course is being established according to The European Cardiologist Association and The American Cardiologist Board recommendations [6] on the grounds of systemic clinical, laboratory and instrumental methods. Under the treatment of the patients, the drug groups were used according to The European Standards of Treatment of the patients with coronary heart disease and the personality traits of the clinical course of the disease. All the patients were under the basic therapy including anticoagulants, disaggregants, statins, inhibitor of the angiotonin transmuting (converting) ferment and the anti-angiogenic medications if needed.

The control group is represented by 21 patients with coronary heart disease obtaining the clinical evidence of the stable angina. As could be observed from the Table 1 both patients' groups were correlated by the age (accordingly ($53, 9 \pm 2, 8$) and ($56,2 \pm 1,9$) years; $p > 0,05$), sex, comorbidity, the main risk factor and the early rate of cholesterol.

Table 1. The characteristics of the patients being examined

Index	Patients with Acute coronary syndrome ($n=20$)	The control group ($n=21$)
Average age ($M \pm m$), years	$53,9 \pm 2,8$	$56,2 \pm 1,9$
Men/women	18/2	18/3
Arterial hypertension	80,0 %	76,2 %
Diabetes	20,0 %	19,0 %
Obesity	20,0 %	19,0 %
Myocardial infarction in anamnesis		
Non Q-infarct	15,0 %	14,3 %
Q-infarct	10,0 %	14,3 %
In-patient clinic treatment		
Aspirin	95,0 %	85,7 %
Clopidogrel	85,0 %	9,5 %
Unfractionated or low-molecular heparin	75,0 %	-
β -adrenoceptor blocking agent	80,0 %	76,2 %
Inhibitors of angiotensin converting enzyme	85,0 %	85,7 %
The rate of chondroitin sulphate before treatment ($M \pm m$), Mmol/l	$5,66 \pm 0,06$	$6,15 \pm 0,10$

The investigation of the antigens of the Herpesviridae family was conducted by the immune fluorescent

method using the polyclonal antiserum against the herpes simplex of the 1st and 2nd type (HSV-1, HSV-2), the human herpes virus of the 6th type (HHV-6), cytomegalovirus (CMV), herpes zoster-chickenpox (VZV) and Epstein Barr virus (VEB).

The object to be examined was the blood taken from the ulnar veins on an empty stomach. The cells CD3⁺, CD4⁺, CD8⁺, CD16⁺, and CD19⁺ were defined by the monoclonal antisubstances by the immunofluorescence method. To define the concentration of serosity IgA, IgM, IgG the widely known method of immunodiffusion in gel was applied. Phagocytic activity of neutrophils was estimated by their ability to take the particles of latex (size is 1,0 μ m produced by "Biosterol", Ukraine). Reducing-oxidizing activity of neutrophils was defined by the unprompted and stimulated nitroblue tetrazolium test. The complement system condition was estimated by the total complement kinetics of the blood serum by the 50% erythrocyte hemolysis [7, 8]. To define the concentration of the circulated immune complex (CIC) in blood was managed by the method of selective precipitation CIC into 3,5 % polyethyleneglycol (PEG 6000) with further determination of the albumin concentration in the precipitation. To examine thoroughly the further immune changes of the patients with coronary heart disease, the group of the corresponding age of 18 practically healthy humans was engaged.

The obtained data was processed on PC by the variational statistics methods with the help of Student's t-measures and certainty index P.

Results and discussion

The indexes of definition of markers Herpesviridae agents prove the high level of infection by viruses of the patients with coronary heart disease, in what connection the simultaneous infection of the blood leucocytes by some agents of this group was discovered. Well, among the patients with the acute coronary syndrome the most often antigens CMV, VEB and HHV6 were indicated, but among the patients with the stable angina - HSV1,2 accordingly. The group of patients with acute coronary syndrome has more obvious abnormality of the left ventricular end-diastolic function what can be a result of a hibernated myocardium having renovated after ischemia abolition. According to the data of the central geodynamics among the patients with acute coronary syndrome the higher rates of the ultimate left ventricular end-diastolic volume was discovered – ($148,40 \pm 3,01$) vs ($134,8 \pm 2,52$) sm of the patients of the control group ($p < 0,005$) and decrement fraction ejection of the left ventricle by 6% accordingly.

Under the immune examination it was discovered the lowering of the leucocytes rate ($6,15 \pm 0,3 \cdot 10^9 / l$ and $6,96 \pm 0,06 \cdot 10^9 / l$ accordingly) of the patients with the ACS comparing to the patients with stable angina; and raising the relative concentration of the lymphocytes ($38,97 \pm 1,22$ %) comparing to the to the patients with stable angina ($35,91 \pm 0,31$ %). Moreover, those patients have the tendency of lowering of CD16⁺ concentration, which can be a consequence of the persistent herpesvirus infection.

Table 2. The main characteristics of the immune status of patients with different clinical forms of the coronary heart disease.

Indexes	Practically healthy (n=18)	ACS patients (n=20)		CC Patients (n=21)	
			p		p
CD3 ⁺ , relative quantity, %	$62,5 \pm 2,5$	$47,3 \pm 2,4$	$< 0,05$	$43,7 \pm 1,8$	$< 0,05$
CD4 ⁺ , relative quantity, %	$37,7 \pm 1,9$	$27,5 \pm 1,6$	$< 0,05$	$20,2 \pm 1,1$	$< 0,05$
CD8 ⁺ , relative quantity, %	$19,3 \pm 1,2$	$19,8 \pm 0,8$	$> 0,05$	$12,1 \pm 0,7$	$< 0,05$
CD19 ⁺ , relative quantity, %	$18,1 \pm 1,4$	$19,6 \pm 0,7$	$> 0,05$	$23,5 \pm 1,8$	$< 0,05$
Correlation of CD4 ⁺ /CD8 ⁺	$1,95 \pm 0,06$	$1,36 \pm 0,02$	$< 0,05$	$1,66 \pm 0,03$	$> 0,05$
BTR with TNF, %	$43,7 \pm 5,02$	$22,1 \pm 3,0$	$< 0,05$	$31,8 \pm 4,7$	$< 0,05$
IgA, (gram per liter)	$1,7 \pm 0,16$	$1,15 \pm 0,08$	$> 0,05$	$2,73 \pm 0,12$	$< 0,05$
IgM (gram per liter)	$1,8 \pm 0,18$	$1,10 \pm 0,05$	$< 0,05$	$1,84 \pm 0,08$	$> 0,05$
IgG (gram per liter)	$12,6 \pm 1,14$	$16,8 \pm 1,2$	$< 0,05$	$14,0 \pm 0,9$	$> 0,05$
Complement, CH50, c.u.	$42,5 \pm 4,36$	$62,7 \pm 3,8$	$< 0,05$	$48,0 \pm 3,1$	$< 0,03$
CIC (gram per liter)	$1,2 \pm 0,08$	$5,9 \pm 0,19$	$< 0,05$	$4,5 \pm 0,3$	$< 0,05$
TNF α , Pg/ml	$41,8 \pm 4,46$	$75,2 \pm 6,83$	$< 0,05$	$62,3 \pm 5,28$	$< 0,05$

Note: $p < 0,05$ – represents the availability of the diversity among the patients indexes and control.

In the populations of CD4⁺ and CD8⁺-T-lymphocytes the evident misbalance is being presented. Lowering of the subpopulation CD4⁺ T-lymphocytes correlates with the lowering of the blasting transformation of lymphocytes in the groups of patients with ACS.

The data of the literature source [5, 7] testify the herpes virus infection is accompanied by such drastically lowering of the CD4⁺ T-lymphocytes which causes reverse correlation of CD4⁺/CD8⁺. The drop of this index till 1,4 indicates the virus forced immune deficiency. The lower helper-suppression correlation is the higher immune deficiency appears to be [7]. The obtained by us results only

confirm this data. The helper-suppression correlation credibly differs from the correlated index of the practically healthy humans and the group of the patients with ACS and is 1,36. Rising of the subpopulation of CD8⁺ and lowering of CD8⁺ is the specific characteristic of the people of the elder age (elder than 50). Following from that the average age of the groups under examination is comparable to the discrepancy discovered immune indexes could be defined as the influence of the herpes virus persistent infection. As the previous researches have showed that, the rate of infection of patients with ACS is really higher than the patients with the stable clinical course of CHD. Due to this, we suppose

the reason of misbalance of the immune competent cells quantity can be the herpes virus persistent infection.

As a rule, pain syndrome and psycho emotional loading which accompanies CHD could be referred to the stress factors. It is well known under the influence of stress factors different by their nature exceeding the physical stimulus limits, the activation of activity of the function of anterior lobe of hypophysis, rising of the secretion by the adrenal glands of the steroid hormones (I.A. Grygorova 1997) can be observed. As to the level of steroid hormones in the blood plasma correlates with the lowering of the immune competent cells and accompanies by the immune suppressive effect. Moreover, the result of that the involution of the lymphoid members and lymphopenia is being observed. According to G.Selye the reaction on stress factor is concerned as stereotypic of somatic evidence of the body defence mobilization. Under ACS because of the special features of its clinical presentation the adaptation to the damaging agents is lower than while the stable clinical course of CHD [9, 10]. That is also could be one of the reasons more significant of lymphocytes' population lowering in the group of patients with ACS. However, it should be mentioned the immune response can be formed either by the factors connected with the main disease, probable associated pathology, or both by the sex and age of patients. In connection with the big quantity of the immunogenic factors but often differently directed – as the changes in the immune status could be a result of a complex many factored influence with the formation of immune syndromes and the tendencies of the immune response [2, 5].

Moreover, when the immune status is being studied it should be taken into account the immune system reaction for the excitation is always patient-specific and genetically conditional. It is possible to get as much of different immune responses for one irritant factor as many patients had been examined. The intensity of the immune response lowers if the influence of the virus antigen coincidences by time with the stress factor. From the other side the integration of the genetic materials of the viruses into genom immune competent cell itself can bring to its incompetence.

Well, the functional activity of the blood lymphocytes determination in the group of the CHD patients examined by us indicated the lowering of their ability to blast transformation. This index of functional activity of the lymphocytes as the response of phytohemagglutinin in two groups of patients under consideration was evidently depressed. In addition, the level of blast transformation of the ACS patients was lower than the same index in the group of patients with the stable angina almost for 10 % and almost twice than the practically healthy persons have. The changes were observed in the phagocytic system which were also accompanied by the level of 5,9 of CIC \pm 0,19 gram per liter ($p < 0,001$) with the formation of hyper immune complex syndrome at patients with ACS is the confirmation of virus-challenged immune disbalance at patients.

When recrudescence of repeated bout of herpes virus infection occurred, the suppression of the reaction of the blast transformation of the lymphocytes is the proven fact. It is quite opposite in the remission period as the lymphocyte transformation increases [4, 7]. However, the clinical

evidence of the herpes virus infection in the groups under examination was not observed. So it was reasonable to expect not the lowering but rising of the blast transformation level. The low ability of the lymphocytes for transformation probably could be explained by the target organ under the repeated bout of herpes virus infection became only endothelium of the vessels and the lymphocytes themselves. As we defined, the antigens of the viruses were defined only in the leucocytes and lymphocytes of the blood. Moreover the average index of the fluorescence for ACS patients exceeded corresponding index of the control group almost by 6 times.

The humoral link indexes analysis also defined the definite peculiarities in the group of ACS patients. However, it should be mentioned that the difference of the immunoglobulin levels and B-lymphocytes wasn't that significant as when the cell link of immune analysis.

Also it is worse saying among the isotopes of immunoglobulin the raise of the IgG levels observed in the groups of patients with ACS, comparing both to the groups of practically healthy persons and patients with the stable angina.

Conclusion. It can be concluded that virus-modified immune disbalance is the background of the clinical course destabilization of the CHD with formation of the acute coronary syndrome.

Patients with the acute coronary syndrome which is proceeding against the background of integrated herpes virus persistent infection have also the depressing of the functional activity of the cell link of immune both growth of the CIC level and the hyper immune complex syndrome forming as well with the lowering of the total complement level.

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ІМУНОЛОГІЧНИЙ ДИСБАЛАНС У ХВОРИХ НА ГОСТРИЙ КОРОНАРНИЙ СИНДРОМ В УМОВАХ ГЕРПЕСВІРУСНОЇ ПЕРСИСТЕНЦІЇ

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Метою роботи було вивчення та оцінка впливу особливостей вірусіндукованого імунологічного дисбалансу на перебіг ішемічної хвороби серця, яка розгортається на тлі персистуючої герпесвірусної інфекції. Обстежені 41 хворий на CHD: 20 пацієнтів з гострим коронарним синдромом та 21 – із стабільною стенокардією, співставні за статтю та віком. Встановлено, що вірус індукований імунологічний дисбаланс є підґрунтям для дестабілізації перебігу CHD з формуванням гострого коронарного синдрому та характеризується пригніченням функціональної активності клітинної ланки імунітету, а також підвищенням рівня ЦІК з формуванням гіперімуннокомплексного синдрому та зниженням рівня загального компліменту.

Ключеві слова: гострий коронарний синдром, герпес віруси, імунологічний дисбаланс

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ИММУНОЛОГИЧЕСКИЙ ДИСБАЛАНС У БОЛЬНЫХ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ В УСЛОВИЯХ ГЕРПЕСВИРУСНОЙ ПЕРСИСТЕНЦИИ

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Целью работы было изучение и оценка влияния особенностей вирусиндуцированного иммунологического дисбаланса на течение ишемической болезни сердца, развивающейся на фоне персистирующей герпесвирусной инфекции. Были обследованы 41 больной ИБС: 20 больных острым коронарным синдромом и 21 – стабильной стенокардией, сопоставимые по полу и возрасту. Установлено, что вирусиндуцированный иммунологический дисбаланс является основанием дестабилизации течения ИБС с формированием острого коронарного синдрома и характеризуется угнетением функциональной активности клеточного звена иммунитета и повышением уровня ЦИК с формированием гипериммунокомплексного синдрома и падением уровня общего комплемента.

Ключевые слова: острый коронарный синдром, герпесвирусы, иммунологический дисбаланс

IMMUNOLOGICAL DISBALANCE AT PATIENTS WITH ACUTE CORONARY SYNDROME IN THE CONDITIONS OF HERPETIC PERSISTENTION

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The purpose of work was a study and estimation of influencing of features of virus induced of immunological disbalance on the case of ischemic heart trouble, developing on a background persisting herpetic infection. Were inspected 41 patient with ischemic heart disease, 20 patients with a acute coronary syndrome and 21 – stable stenocardia, comparable on a sex and age. It is set that virus induced an immunological disbalance is foundation of destabilization of stream of ischemic heart disease with forming of sharp coronary syndrome and characterized oppressing of functional activity of cellular link of immunity and increase of level circulating immune complexes with forming of hyperimmune syndrome and decreasing of level of general complement.

Keywords: acute coronary syndrome, herpesvirus, immunological disbalance

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