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STATE OF THE CYTOKINE PROFILE AND APOPTOSIS FACTORS OF CHILDREN WITH DILATED CARDIOMYOPATHY

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ABSTRACT

A clinical and immunological examination of 21 school children from 7 to 14 years old with dilated cardiomyopathy (DCMP) was carried out. As a control, 20 practically healthy children of comparable age were examined. Significant changes in the studied parameters of the immune system were found in children with DCMP. A significant increase in the concentration of pro-inflammatory (TNF-α and IL-18 increased by 4.2 and 3.0 times) cytokines was revealed. The number of expressing apoptosis antigen - CD95 + cells in peripheral blood rises 2.0 times.

KEYWORDS: children, dilated cardiomyopathy, immunity, lymphocytes, apoptosis, cytokines.

INTRODUCTION

In recent years, a wide study of apoptosis processes in the development of pathological processes has begun. This problem is relevant, reveals the importance of the activation of apoptosis factors in dilated cardiomyopathies (DCMP) in children. DCMP is a disease characterized by dilatation of the left ventricle with the development of systolic heart failure and is not associated with coronary heart disease or valvular dysfunction.[3,4,9,12]

Apoptotic cell death is known to be a fundamental process in regulating immune responses. The classic specific apoptosis induction receptor is CD95 + (Fas / Apo-1). When cells are activated, CD95 + is most expressed on neutrophils, CD4 + T-lymphocytes, which characterizes their high sensitivity to FasL-induced apoptosis, but the action of inducers is necessary to start the process.[1,5] The pro-inflammatory cytokines TNF-α, which is the main pro-apoptogenic cytokine and, at the system level, leads to the induction of apoptosis of blood cells, act as factors inducing apoptosis. Another inducing factor is interleukin-18 (IL-18), which, affects the secretion of IFNγ, activates the cells of the monocyte-macrophage system, which leads to the activation of many antibacterial and antiviral responses. It is believed that the stress-induced release of IL-18 can lead to an increase in the IFNγ cycle, which is involved in the activation of the expression of Fas proteins (CD95 +), the stimulation of which leads to apoptosis.[2,6,7]

The aim of this study was to study the state of the cytokine profile and apoptosis factors in schoolchildren with DCMP.

MATERIAL AND METHODS

The present study included 50 schoolchildren from 7 to 14 years old with an established diagnosis of DCMP. The control group consisted of 20 children of the same age.

Immunological studies in the examined children were carried out in the laboratory of immunoregulation of the Institute of Human Immunology and Genomics, Academy of Sciences of the Republic of Uzbekistan.

The expression of CD95 + receptors was performed using monoclonal antibodies produced by Sorbent LLC, Russia (Moscow).

The concentration of tumor necrosis factor-α and interleukin 18 (TNF-α and IL-18) in the blood serum was determined by the method of enzyme-linked immunosorbent assay using test systems ZAO "VECTOR-BEST" (Russia, Novosibirsk). Quantitative assessment of the results was carried out by constructing a calibration curve or using the commercial computer program “Microplate manager”, reflecting the dependence of optical density on concentration for a standard antigen and allowing comparison of the studied samples with it.

Statistical processing of the obtained data was carried out using the computer program Statistica 6.0. The

significance of differences in the average values of the compared indicators was evaluated by Student's criterion (t)

RESULTS AND DISCUSSION

Apoptosis, often called physiological cell death, is an energetically active, genetically controlled process that serves to eliminate defective or damaged cells. Apoptosis helps preserve the order and normal functioning of the biological system, cleansing of unclaimed, sick (who have completed their life cycle or resulting from mutations of potentially dangerous) cells and is a fundamental process of maintaining homeostasis: both an increase and a decrease in the level of apoptosis lead to disruption of homeostasis and the development of various diseases. IL-18 and apoptosis expressing antigen - CD95 + lymphocyte cells are involved in the process of initiating programmed cell death.

Interleukin 18, being a pleiotropic pro-inflammatory cytokine, stimulates the production of IFNγ, TNFα, IL-1, IL-2, apoptosis factors, increases the proliferative activity of T-lymphocytes, increases the lytic activity of NK cells. IL-18 is involved in the formation of cellular and humoral[6,7,8], innate and acquired immune responses[14], stimulates the production of adhesion molecules that are involved in the mechanisms of cell migration, which is important both in the formation of the immune response and in pathogenesis of certain diseases.[13]

IL-18 not only stimulates the synthesis of INFγ, but also modulates its functional activity. It was shown that the expression of the Fas ligand of CD4 + Th1 and NK cells also occurs under the influence of IL-18. On the other hand, it was shown that INFγ is involved in the activation of expression of Fas itself. Thus, we can conclude that IL-18 alone (FasL) or through INFγ (Fas) stimulates the initialization of apoptosis.[8]

In the peripheral blood serum of healthy children, the level of IL-18 ranged from 27 to 68 pg / ml, and averaged 48.3 ± 2.84 pg / ml. A study of the production of IL-18 showed a 3.0-fold increase in children with DCMP (146.3 ± 9.00 pg / ml, P <0.001) in comparison with the control group (Table 1.).

Table 1: The number of CD95 cells and the concentration of certain cytokinesin children, (M±m).

Indicators	Control Group n=20	DCMP n=21	P
IL-18 pg/ml	48,3±2,84	146,3±9,00	P<0,001
TNF-α pg/ml	12,5±0,96	52,3±2,70	P<0,001
CD95 %	18,8±0,91	38,5±1,44	P<0,001

An increase in the concentration of IL-18 can lead to activation of the expression of Fas proteins (CD95), the stimulation of which leads to apoptosis.

The binding of soluble and surface-expressed activated lymphocyte receptors (FasL- and Fas-) causes cell apoptosis. The number of peripheral blood-expressing apoptosis antigen - CD95 + cells in healthy children averaged 18.8 ± 0.91% with individual values from 11 to 24%. This indicator in children with DCMP was significantly increased (38.5 ± 1.44% P <0.001) compared with those of healthy newborns.

An increase in the expression of apoptosis antigen - CD95 + cells in the peripheral blood, which refers to a membrane or receptor-mediated factor, initiates the development of apoptosis. Through the C-terminal intracellular domain of this receptor (the so-called death domain), the implementation of the apoptogenic signal is activated. The determination of CD95 + on the surface of lymphocytes is regarded as their readiness for apoptosis.

The next stage of our research was to determine the level of TNF-α in blood serum in children.

We conducted a study to determine the level of production of TNF-α as an important mediator, which is one of the most universal regulators of immunity and inflammatory reactions with a wide range of biological effects. The main producers are monocytes and macrophages. It is also secreted by neutrophils, endothelial and epithelial cells, eosinophils, mast cells, B and T lymphocytes when they are involved in the inflammatory process.[7,8]

TNF-α normally plays a fundamental physiological role in immunoregulation, but in some cases it can exert a pathological effect, taking part in the development and progression of inflammation, microvascular hypercoagulation, hemodynamic disturbances and metabolic depletion (cachexia) in various human diseases, both infectious and non-infectious nature[10], including heart disease. A direct relationship was established between TNF-α and heart failure syndrome, which means that the level of TNF-α in the serum of patients with severe heart failure is an order of magnitude higher than in healthy individuals.[11,15]

An analysis of the results showed that in healthy individuals, individual indicators of TNF-α production ranged from 7 to 20 pg / ml, and the average value of this cytokine was 12.5 ± 0.96 pg / ml. Thus, the level of the pro-inflammatory cytokine TNF-α was significantly increased in the main group of patients (P <0.001) and averaged 52.3 ± 2.70 pg / ml.

The ratio of the increase in the concentration of TNF-α cytokine relative to the control values in patients with DCMP was 4.2 times. The data obtained suggest that there is a certain dependence of the level of TNF-α concentration on the nature of the pathological process, as evidenced by the very high level of its production in the main group.

Our studies have shown that in children with DCMP there is a significant increase in the concentration of pro-inflammatory (TNF-α and IL-18 increase by 4.2 and 3.0 times) cytokines. The number of expressing apoptosis antigen - CD95 + cells in peripheral blood rises 2.0 times.

The level of TNF-α and IL-18 can indirectly judge the activity of the inflammatory process as a whole. It is likely that there is a positive correlation between the severity of cardiac pathology and the level of synthesis of TNF-α and IL-18, and the heavier the heart failure, the stronger the response of the immune system and the higher the level of cytokines, and vice versa.

Our data suggest that as a result of a critical increase in the level of circulating pro-inflammatory cytokines, one after another processes that have negative cardiovascular effects are activated, which subsequently contribute to even greater damage to the myocardium.

Thus, elevated levels of TNF-α, as well as IL-18 progressively have a direct damaging effect on cardiomyocytes, inducing their apoptosis. Given the great importance of mediators in providing the entire mechanism for protecting the body from infectious and other antigens, it can be considered highly relevant to conduct a study of the level of pro-inflammatory cytokines in heart failure in children with DCMP.

CONCLUSIONS

1. It was revealed that in children with DCMP, the level of pro-inflammatory cytokines was significantly increased, and this fact allows us to judge the activity of the inflammatory process, which progressively has a direct damaging effect on cardiomyocytes. So, in children of the main group, the synthesis of TNF-α and IL-18 is increased by 4.2 and 3 times, respectively, than in children of the control group.

2. It has been established that in children with DCMP, a significant (2.0-fold) increase in the number of CD95 + cells expressing apoptosis antigen occurs in peripheral blood.

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