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FEATURES OF BALANCE OF PROINFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES IN NEWBORNS WITH HERPES VIRUS INFECTIONS

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The paper examines features of balance between proinflammatory and anti-inflammatory cytokines in newborns of mothers with herpes virus infections (SHV, CMVI). This investigation included 35 newborns, of them 10 were full-term newborns of healthy mothers (group 1 - umbilical blood); 10 - full-term newborns with various pathology of perinatal period in mothers with intrauterine infections (group 2 - umbilical blood); 15 practically healthy newborns of healthy mothers (control group - peripheral blood). The paper studies production of proinflammatory IL-1b, IL-8, γ-IFN and anti-inflammatory (IL-4) cytokines in newborns in norm and with intrauterine infections.

The study has shown that the level IL-4 in the umbilical blood in newborns born from the mothers with intrauterine infection did not differ from a level in peripheral blood of healthy newborns. It has found also that there was 1.5 times increase of IL-1b in newborns with intrauterine infection in the umbilical blood in comparison with umbilical blood in healthy newborns, 3.4 times increase in IL-8 and the tendency to increase IFN-gamma.

Keywords: Cytokines, interleukins, interferon.

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The has been increasing interest to study cytokines which are humoral factors of intercellular interactions. Cytokines representing proteins and being developed mainly by activated cells of immune system, provide intercellular cooperation, positive and negative immunoregulation of body's defense system (Simbirtcev, 2004; Freidlih, 2001). The study of the cytokine levels in various diseases is based on their key factors of immunogenesis in many immunodeficit conditions (Umarova, 2009).

The cytokines, as it is known, are traditionally subdivided into several groups: interleukins (IL) - factors of interaction between leucocytes; interferons (IFN) - cytokines with antiviral activity; the tumor necrosis factors (TNF), cytokines, strengthening cytotoxic activity; colony-stimulating factors - hemopoietic cytokines; hemotoxic cytokines (Ignatov, 2002; Yarlin, 1997).

In the process of recognition and representation of antigens by macrophages there is an increase of proinflammatory cytokine concentration: interleukine - 1b (IL-1b), and interleukine-8 (IL-8), that are necessary for activation, growth and differentiation of lymphocyte; changes of the neutrophile functional state. The increase of proinflammatory cytokine levels causes development of system inflammatory reaction. The study of functional activity of the interferon system in newborns revealed ability of umbilical cord blood cells to produce IFN-ά, and IFN-γ in concentrations comparable with the adults. At the same time, a great number of various factors effect the activity of interferon system of the fetus and newborn infant. Accordingly, it was noted, that mother's extragenital pathology and complicated course of pregnancy can disrupt functioning of the interferon system (Neceevskaya, 2000). The works studying influence of intrauterine infection with herpes virus, chlamydia on the functional state of the interferon system in newborn are few and contradictory (Koroleva, 2007; Gibson et al., 2004).

A number of studies showed that the ability to an increased production of interferon allows a newborn to avoid the development of infectious disease either with intrauterine or bacterial infection (Kravchenko, 2008; Zdravkovic et al., 1997). Moreover, Volodin et

al. (2000) found out that newborn children with heavy intrauterine infection had low concentration of IL-6 and high levels of IL-8 during the first weeks of life. It was noted also, that the increase of IL-4 level in healthy newborns provided the balance of proinflammatory and anti-inflammatory cytokines; this physiological condition constrained development of clinical picture of systemic inflammation.

The literature observation generally indicates on the necessity for further complex study of cytokine profile in newborns with intrauterine infections.

The purpose of the present work was to study the features of balance between proinflammatory and anti-inflammatory cytokines in newborns born to mothers with herpes virus infections (SHV, CMVI).

Material and methods

This investigation included 35 newborns, of them 10 were full-term newborns of healthy mothers (group 1 - umbilical blood); 10 full-term newborns with various pathology of perinatal period of mothers with intrauterine infections (group 2 - umbilical blood); 15 essentially healthy newborns of healthy mothers (control group - peripheral blood).

The newborns of the second group were born to the mothers with associated herpes virus and cytomegalovirus infection. The study of newborns was carried out in the Scientific Research Institute of Obstetrics and Gynecology and in the branch of neonatal pathology of the urban children's hospital No5. The identification of the diagnosis was made through immunoenzymatic assay (IEA) for the presence of specific antibodies and polymerase chain reaction (PCR).

There were carried out investigations of the production of proinflammatory (IL-1b, IL-8 and γ-IFN) and anti-inflammatory (IL-4) cytokines both in newborns in norm and in intrauterine infections. The principle of the testing system for cytokine identification is based on a "sandwich» method of solid-phase enzymatic-immunoanalysis with application of horse-radish peroxidase as fermentative indicator. Quantitative estimation of the results performed using constructing calibrated curve or commercial computer program "Microplate manager;" these methods allowed to observe dependence of optical density on concentration of a standard antigen and also they provided comparison with the studied samples. Sensitivity of a method was 5-30 pg/ml.

Results and discussion

This work presents the results of study of cytokine production in the peripheral blood serum and umbilical cord blood serum in newborns.

During measurement the IL-1b concentration level in control group (peripheral blood) varied within 128.0-280.0 pg/ml and made on average 200.5±11.10 pg/ml. The synthesis of IL-1b in umbilical blood serum in newborns of healthy mothers was reliably reduced; it made 117.4±8.35 pg/ml ($P<0.05$). The concentration of this monokine in umbilical blood serum of newborns of mothers with intrauterine infections had no significant differences from control values in the peripheral blood of healthy newborns; it made 179.8±8.20 pg/ml. This parameter in the umbilical blood was 1.5 times higher than in infants born to healthy mothers ($P<0.05$).

The data received suggest for presence of certain dependence of IL-1b production level from the character of pathological process; this was confirmed by increase of IL-1b in intrauterine infection.

It is known, that IL-8 intensifies intracellular microorganism death and promotes their elimination. Average level of IL-8 in the peripheral blood serum in healthy newborns was 181.3±7.42 pg/ml with variations from 130 up to 220 pg/ml. IL-8 level in the umbilical blood in infants born to mothers with intrauterine infections was reliably higher of the level in comparison with umbilical blood in newborns of healthy mothers (119.5±26.7

pg/ml vs. 34.8±3.45 pg/ml, P<0.05); it was reliably lower of control level in peripheral blood in healthy newborns (119.5±26.7 pg/ml vs. 181.3±7.72 pg/ml, P<0.05).

The IL-8 synthesis can be induced by other cytokines (IL-1b and TNF), bacterial and viral products. Probably, its increase in the umbilical blood in newborns born to women with intrauterine infection is related to this fact.

As to anti-inflammatory cytokine IL-4, its level in the umbilical blood in practically healthy newborns was 26.2±2.08 pg/ml which was reliably lower than the parameters in other groups (P<0.05). IL-4 level in the peripheral blood increased and made on average 60.1±4.43 pg/ml; variations were 35-90 pg/ml.

The IL-4 level in the umbilical blood in newborns of mothers with intrauterine infections did not differ from the level in peripheral blood serum of healthy newborns.

The interferon system is aimed at detection and elimination of foreign genetic information. The most important function of γ-IFN is its participation in regulation of interrelations between lymphocytes and macrophages, as well as in regulation of cellular and humoral immune responses.

The study showed that average concentration of γ-IFN in peripheral blood serum in healthy newborns was 25.2±1.94 pg/ml; it remained the same in umbilical cord blood of children in the first group. In the umbilical cord blood of the second group the level of gamma-IFN tended to increase (30.2±2.26 pg/ml), but had no reliable differences from parameters of other groups (Table 1).

TABLE 1.LEVEL OF CYTOKINES IN THE SERUM OF PERIPHERAL AND UMBILICAL CORD BLOOD OF NEWBORNS

	Control-peripheral blood n=15	Umbilical blood				
		Group 1 n=10	Group 2 n=10	P_1 C-G1	P_2 C-G2	P_3 G1-G2
IL-1b	200.5±11.1	117.4±8.35	179.8±8.20	P<0.05	P>0.05	P<0.05
IL-4	60.1±4.43	26.2±2.08	59.7±4.64	P<0.05	P>0.05	P<0.05
IL-8	181.3±7.42	34.8±3.45	119.5±26.7	P<0.05	P<0.05	P<0.05
γ-INF	25.2±1.94	24.7±2.51	30.2±2.26	P>0.05	P>0.05	P>0.05

As a result, newborns with intrauterine infections in the umbilical cord blood had 1.5 times rise of IL-1b in comparison with healthy newborns; accordingly they had 3.4 times increase of IL-8, they had a tendency to increase of IFN-gamma as well. It can be assumed that a cytokine disbalance can be one of the reasons of inflammatory process enhancement in intrauterine infections.

This study concludes findings described in our previous works (Rakhamankulova, 2009a; 2009b). It was established previously that newborns with intrauterine infections in early neonatal period had, in addition to leucocytosis and lymphocytosis, also reliable decrease of total number of T-lymphocytes and T-helpers/inducers. The newborns had a tendency to decrease for the quantity of natural killers, T-suppressor/cytotoxic lymphocytes; and a tendency to increase for the quantity of cells with the receptor to apoptosis (CD95+). Further, a deep disbalance in parameters of T-cellular immunity is found in the late neonatal period; it is expressed in significant deficit of T-lymphocytes, T-helpers, T-suppressors, and natural killers. The reliable increase of CD95+ in the peripheral blood of newborns in intrauterine infection in the late neonatal period may be an indication of strengthening the process of apoptosis process in the cells damaged by viruses. The contents of immunoglobulins of the main classes IgG, IgM, IgA were significantly increased in comparison with the control (Rakhamankulova, 2009a; 2009b).

Nowadays some main reasons of the development of immunodeficit states have become clear. The disturbance of immunoregulatory processes developed with the participation of Th1 and Th2-helpers in the body under various agents, including viruses, is one of such reasons. As it is known, the first synthesized cytokines stimulate cellular immunity (IL-1b, 2, 6, 8, 12, IFN, TNF etc.); the second synthesized cytokines stimulate humoral immunity

(IL-4, 5, 10, transforming growth factor-better etc.). In the normally functioning body there is a certain balance of interaction between Th-1 and Th-2-helpers. But the strong change of their activity under the influence of any effect can lead to serious adverse consequences in functioning of immune system as a whole. It is established that the infectious process causes activation of Th2-helpers and cytokine synthesis, resulting suppressive effect on cellular immunity.

Furthermore, infectious process damages phagocytary activity of monocytes /macrophages, it also distorts one more their important function - antigen presenting, i.e. ability to represent foreign antigenic determinant in complex with their HLA-DR and HLA-DQ antigens to T- and B - lymphocytes. This process appears as starting of the cellular and humoral immune response development. Essential reduction of expression of HLA-DR and HLA-DQ of antigens on these cells lead to reduced ability of the body to develop specific immune response.

References

Freidlih, I., Totolyan, A., 2001. "The nuclear of immune system," S-Pb: Nauka.

Ignatov, P., 2002. Immunity and Infection, Moscow, Vrema (the Time), pp.97-105.

Koroleva, A., 2007. "The characteristic features of functional system of interferon on mothers and their newborn babies which are infected with intra nuclear viruses," Pediatria (The Pediatrics), Vol.86, No1, pp.20-25.

Kravchenko, L., 2008. "The state of immune system in babies with the infection of the herpes virus in first months of life," Pediatria (The Pediatrics), No1, pp.52-58.

Neceevskaya, M., 2000. Clinical and immunological criteria of the forecasted gestosis, Synopsis of doctoral dissertation, Moscow.

Rakhmankulova, Z., 2009a. "Specific characteristics of the development of immune system in newborns with intrauterine infections in the early neonatal period," Physiology and pathology of immune system, No4, pp.27-32.

Rakhmankulova, Z., 2009b. "The development of immune system in newborns with intrauterine infections in the late neonatal period," Physiology and pathology of immune systems, No5, pp.22-29.

Simbirtcev, A., 2004. "The importance of cytokines in regulation of physiological functions of the immune system," Physiology and pathology of immune system, No10, pp.3-10.

Umarova, A., 2009. The Aspects of Cytokines in the cases of immunological deficits in various degrees of genesis, Synopsis of doctoral dissertation, Tashkent.

Volodin, N., Degtareva, M., Simbirtceva, A., Kotov, A. et al., 2000. "The importance of inflammatory and anti-inflammatory cytokines in the cases of immunological adaptation of newborn babies," International Journal on Immunorehabilitation, Vol.2, No1, pp.175-85.

Yarilin, A., 1997. "The System of Cytokines and Principles of its Functioning in Normal and Pathological cases," Immunologia (The immunology), No5, pp.7-14.

Zdravkovic, M, Knudsen, H., Liu, X., Hager, H. et al., 1997. "High interferon alfa levels in placenta, maternal, and cord blood suggest a protective effect against intrauterine herpes simplex virus infection," L Med Virol., Vol.51 (3), pp.210-213.