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ABSTRACT

of the dissertation submitted for the degree of Doctor of Philosophy

GENETIC ASPECTS OF IMMUNE RESPONSE TO LOCAL INFECTIOUS-INFLAMMATORY DISEASES AND SEPSIS IN INFANTS

Specialty: 3244.01 – Allergology and immunology

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GENERAL CHARACTERISTICS

Relevance of the research. The number of patients with allergic pathology, including local infectious-inflammatory diseases and sepsis, increases every year[1,2,3]. Local infectious-inflammatory diseases and sepsis are primarily related to the influence of environmental factors and the genetic predisposition of the organism[4]. Local infectious-inflammatory diseases and sepsis are quite common in babies[5,6]. They have a special place among the aggravated diseases with severe clinical course and cause of death. In recent years, sepsis has become more common in infants, as well as in adults. Despite the availability of new broad-spectrum antibiotics and antiseptics, the number of patients with sepsis has increased tenfold in the last 50 years. It is known that sepsis usually develops after a local inflammatory process. Recent researches show that the local inflammatory process leads to sepsis only when the body's immune system is weakened.

However, the modern literature on immunology does not contain specific data on the effect of any premorbid background on the infants' immune system during local infectious-inflammatory diseases.

There is also no information on the transformation of local

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[2] Glushenko V.A. (2017). The structure of nosocomial infections in a multidisciplinary hospital. *Chief Physician* (*5-6),* 40 - 43.

[3] Brown, G. D., Willment, J.A ., Whitehead, L. (2018). C-type lectins in immunity and homeostasis. *Nature Reviews Immunology (18),* 374 - 389.

[4] Glinsburg A. L. et al. (2010). Exogenous and endogenous factors in the pathogenesis of atherosclerosis. *Russian Journal of Cardiology (2),* 92 - 96.

[5] Svistushkin V. M. (2017). Bacterial infections of the ENT organs: subtle therapy. *Medical Advice (8),* 58 - 63.

[6] Redegeld, F. A ., Yu, Y ., Kumari, S ., Charles, N ., Blank, U. (2018). Non-IgE mediated mast cell activation. *Immunol. Rev. (282),* 87 –91.

inflammatory diseases into sepsis as a result of harmful socio-biological factors.

In the last 20 years, special attention has been paid to the role of dysbacteriosis in the intestinal cavity when considering the transformation of local inflammatory processes into sepsis. In both diseases, it is observed a dysfunction of the immune system and a decrease in the body's defense ability, which in turn can lead to the transformation of local inflammatory processes to sepsis. Despite the fact that lipid peroxidation of cell membranes and the products of these reactions cause some degree of damage to the immune system, the pathogenetic mechanism of the transformation of the local inflammatory process to sepsis has been poorly studied. On the other hand, in the treatment of local inflammatory processes and sepsis, to date, only antibiotics, immunotropic drugs and measures aimed at eliminating intoxication are used. Still, due to the fact that complete clinical - immunological and metabolic recovery is not always observed, it encourages clinicians, immunologists - allergists, pathophysiologists and other specialists to develop and apply new methods of treatment of this disease. There is very little information in the literature on the treatment and prevention of local inflammatory diseases and sepsis, depending on the premorbid background of one or other immuno-metabolic changes in babies. In addition to the lack of information, they are also contradictory, which confirms the need and importance of relevant research in this area.

Undoubtedly, the pathogenesis of sepsis is based on the activation of a cytokine cascade, which includes both anti-inflammatory products and anti-inflammatory cytokines. The balance between these opposite groups of mediators determines the nature and outcome of purulent-septic diseases[7,8].

[7] Cayrol, C.; Girard, J.-P. (2018). Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family. *Immunol. Rev. (281)*,154 – 168.

[8] Wojcik-Pszczola K., et al.. (2018). Connective tissue growth factor regulates the transition of primary bronchial fibroblasts to myofibroblasts in asthmatic subjects. *Cytokine (102)*, 187 – 190.

Thus, in recent years, the search for new markers of sepsis, which allows diagnosing the disease at an early stage, assessing its severity, monitoring the treatment and predicting the outcome, is becoming increasingly relevant. In view of the abovementioned, we have set ourselves the goal of conducting the current research.

The aim (purpose) of the research:

The aim of the study is to substantiate the role of some socio-biological factors, infant nutrition, intrauterine development, thymomegaly, dysbacteriosis, ARVI (acute respiratory viral infection), transformation of local infectious-inflammatory diseases into sepsis in infants, and argumentative approaches to treatment.

To achieve these goals, we have planned a series of solutions to the following tasks:

OBJECTIVES:

1. To group patients taking into account the clinical course of local infectious-inflammatory diseases, their anamnestic data and the characteristics of the premorbid background.
2. To explore three indicators of the immune system – cellular immunity, humoral immunity and phagocytosis of neutrophils, taking into account the premorbid background in the clinical dynamics of local infectious-inflammatory diseases and sepsis in infants.
3. To determine the value of IgG fractions in the development of local infectious-inflammatory diseases and sepsis in infants.
4. To identify the amount of circulating IgE (circulating immune complexes in the blood) in the blood in order to clarify the role of allergens in the pathogenesis of local infectious-inflammatory diseases and sepsis in infants.
5. To develop reliable diagnostic criteria for determining the level of risk of transformation of local infectious-inflammatory diseases into sepsis and assessing the probability of positive or negative outcome of the pathological process on the basis of clinical-immunological and metabolic parameters of the dynamics of the pathological process.

6. Additionally, to compile appropriate diagnostic and prognostic schedules that can be recommended for the daily practice of immunologists predicated on the results obtained.

Scientific novelty of the research:

For the first time, a comprehensive study of the propensity to develop respiratory diseases in infants has been conducted based on 3 polymorphisms of genes of anti-inflammatory cytokines using modern molecular-biological methods.

The obtained data open up additional possibilities in the assessment of predictors of development of bronchopulmonary pat hology in infants. These predictors can serve as an objective criterion for the formation of a risk group for lung diseases in infants.

It has been established that immunological parameters in infants play an important role in the development of local infectious-inflammatory diseases and sepsis. Reliable criteria in this case may be immune parameters (CD4 +, CD16 +, LBRT, IgG2, IgG4 subpopulations).

There is a certain correlation between changes in these indicators and the clinical course of the disease. The nature of the premorbid is of great importance in this interaction.

It was found that an early criterion for the favorable course of sepsis may be an increase in serum IgG concentration in the dynamics.

In this case, in patients with severe sepsis, the movements in the serum concentrations of total IgG and its subclasses are unidirectional, and their arithmetic mean parameters are reduced to a high degree of accuracy compared with the relevant data in healthy infants.

Practical significance of the research:

Based on the analysis of laboratory data, it was determined that the degree of expression of allergies in the body plays a crucial role in the development of local infectious-inflammatory diseases and sepsis. The obtained data open up additional possibilities in the assessment of predictors of development of bronchopulmonary pathology in infants. These predictors can serve as an objective

criterion for the formation of a risk group for lung diseases in infants. Reliable criteria in this case may be immune parameters (CD4 +, CD16 +, LBRT, IgG2, IgG4 subpopulations). Early criteria for the favorable course of sepsis may be an increase in serum IgG concentration in the dynamics. To develop reliable diagnostic criteria for determining the level of risk of transformation of local infectious-inflammatory diseases into sepsis on the basis of clinical-immunological and metabolic parameters of the dynamics of the pathological process and assessing the probability of positive or negative outcome of the pathological process. To compile appropriate diagnostic and prognostic schedules that can be recommended for the daily practice of immunologists based on the results obtained.

The main provisions of the defense:

1. Immunological parameters in infants play an important role in the development of local infectious-inflammatory diseases and sepsis. Reliable criteria in this case may be immune parameters.
2. Early criteria for the favorable course of sepsis may be an increase in serum IgG concentration in the observed dynamics.

3.In infants, the indicators of cellular immunity during local infectious-inflammatory diseases are subject to certain changes depending on the premorbid background.

4.Genetic factors also play an important role in the development of local infectious-inflammatory diseases and sepsis..

5.The correlatons found between congenital and adaptive immunity indecatore reflect the suppression of the carly stages of the immune response and impaired immune regulation in infarts with generalized LİİD and sepsis.

Approbation of the research:

The dissertation materials were discussed at scientific meetings and seminars at the Institute of Genetic Resources of the

Azerbaijan National Academy of Sciences (ANAS) (2013-2017). The main provisions of the dissertation were presented at IV Azerbaijan National Congress of Allergology, Immunology and Immunorehabilitation (Baku, 2012). Preliminary discussion of the dissertation was held on January 26, 2018 at the meeting of the Scientific Council of the Institute of Genetic Resources of the Azerbaijan National Academy of Sciences (Protocol 2).

Publications:

10 articles and 2 theses were published in scientific journals and conference materials of allergists and immunologists on the main theoretical provisions of the dissertation and the results of the research.

Volume and structure of the dissertation:

The research work has been written on 159 computer pages (188818 symbols) and consists of an introduction (13460 symbols). literature review (55190 symbols), research materials and methods (8940 symbols), 3 chapters of personal research (60770+12286+13422 symbols), conclusion, results, practical recommendations (24750 symbols) and a list of cited literature, which includes 174 references. 5 Azerbaijan, 57 of the references are in Russian and 112 in English. The research work has been illustrated with 16 tables and 8 figures.

RESEARCH MATERIALS AND METHODS

The research work was carried out on the basis of Children's Clinical Hospital No. 2 named after A.Garayev and the Institute of Genetic Resources of ANAS in 2010 - 2016.

The research objects were infants with local infectious-inflammatory diseases and sepsis. There were 487 infants with local infectious-inflammatory diseases under our supervision. 60 practically healthy infants were selected for comparison of immune-metabolic parameters.

These infants were divided into 3 groups regarding their ages: Group I – 20 infants aged 1 to 6 months; Group II – 20 infants aged 7 to 12 months; Group III – 20 infants aged 1 to 3 years.

1. T-lymphocytes and their subpopulations (CD3 +, CD4 +, CD8 +, CD14 +, CD16 +, CD19 +) have been identified for the study of the state of cellular immunity using multichannel antibodies. It is currently considered the most reliable research. A blast transformation reaction was used to determine the functional activity of lymphocytes.

2. In order to study the state of the humoral immune system, the amount of immunoglobulins A, M, G in the serum was determined using the enzyme-linked immunosorbent assay (IgG1, G2, G3, and G4). Serum IgE levels in the blood were determined by enzyme-linked immunosorbent assay using "Pharmacia Diagnostic AB" reagents by Swiss company.

Table 1. Characteristics of age and gender composition of infants with local infectious-inflammatory diseases and sepsis

Name	percentage	age (months)			gender	
		1 – 3	4 - 6	7 - 12	m	f
Sepsis	180	71	62	47	108	72
	%	39.4	34.4	26.1	60	40
Local infectious-inflammatory diseases	487	182	155	150	272	215
	%	37.3	31.8	30.8	55.8	44.1
Healthy	40	10	10	20	23	17
	%	25	25	50	57.5	42.5

Note: Percentage is the percentage of the total number of patients.

In addition to immunoglobulins in the blood serum, small, medium and large molecular protein fractions of circulating immune complexes (CICs) were also identified.

3. The amount of neutrophils in 1 μl of blood was determined to detect non-specific immune indicators.

The functional activity of neutrophils was determined using a nitroblue tetrazolium recovery test (NBT-test).

At the initial stage of the study, the infants were divided into groups as follows to identify the role of prenatal risk factors and premorbid conditions in the transformation of local infectious-inflammatory diseases into sepsis in the postnatal period.

Group I included 16 infants born during physiological childbirth after physiological pregnancy. Group II included 18 infants born as a result of pathological pregnancy, but during physiological childbirth. Group III included 15 infants born to mothers with nephropathy during pathological birth. Grade I and II hypoxic lesions of the central nervous system were found in these infants in the early neonatal period.Group IV included 18 infants whose mothers suffered from nephropathy during pregnancy. These infants also had local infectious-inflammatory diseases and ARVI. Group V included 18 infants born after a pathological pregnancy. They had local infectious-inflammatory diseases against the background of I-III degree thymomegaly. Group VI included 28 infants, who were born during a pathological birth. In these infants, local infectious-inflammatory diseases developed against the background of dysbacteriosis. In addition, some of the sick infants selected for the study of the effects of premorbid diseases and nutrition on the course of local infectious-inflammatory diseases were also grouped according to another principle. These patients were divided into 3 groups. In this case, Group I consisted of infants born after the physiological birth. Their postnatal development was normal, and they, in turn, were divided into 2 subgroups: Subgroup 1A included 15 breastfed infants; Subgroup 1B included 15 artificially-fed infants. Group IIA included 17 infants with local infectious-inflammatory diseases developed on the basis of rickets and anemia. Finally, Group IIIA included 19 infants with local infectious-inflammatory diseases developed on the basis of malnutrition, anemia, and rickets.

The capabilities of the spreadsheet processor Excel 2010 (Microsoft, USA) and application software packages (Megastam and

Statistica 6.0, Stat Soft., USA) were used to create the database and statistically study the empirical data.

During the statistical substantiation of the diversity of the studied groups, the Mann-Whitney U-tests for independent groups and the Wilcoxon test for dependent groups were conducted.

The descriptive statistics are presented in the form of a sample mean and a standard deviation. The Fisher-Irwin Exact test was used to analyze the frequency variation in 2 independent groups. Spearman's rank correlation coefficient was used to estimate the density of the relationship between individual indicators.

Statistical analysis of the results of molecular genetic research, including the analysis of the frequency of occurrence of alleles of genes, genotypes and their combinations and the analysis of combination tables was calculated by the direct calculation method of the frequencies of alleles and genotypes of genes.

The association of genes and genotypes was evaluated on the basis of the OR (odds ratio) calculation, calculating the confidence interval for the OR by 95% (95% CI).

The difference between the series compared to the correct probability level was found to be 95% ($p < 0.05$).The obtained data were processed using biometric methods: the calculation of averages (M + m), the accuracy of the differences on Student's t-test, the differences were considered correct when $p < 0.05$.

In addition to the average mathematical quantity, the individual values of one or another parameter of the functional system were specified to determine whether it deviated from the age limit[9].

Rebrova O. Y. (2002). Statistical analysis of medical data. Application package STATISTICA. M.: MediaSfera, 312, ISBN 5 – The book contains information on the concept of evidence-based medicine.

RESEARCH RESULTS AND THEIR DISCUSSIONS

Our study of the dynamics of local infectious-viral diseases confirms that the influence of antenatal, intranatal and postnatal risk factors on the infant's body is important in the development of these diseases.

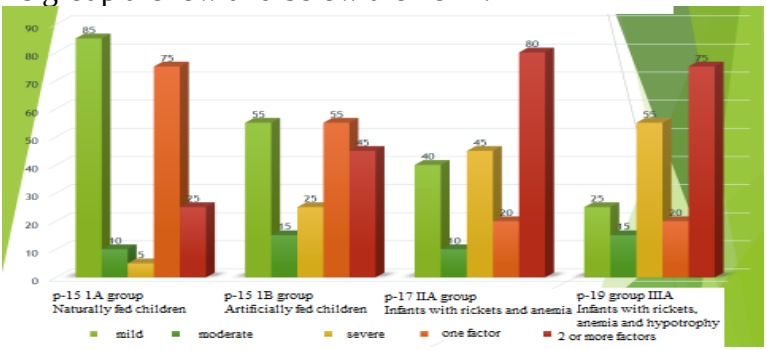
The role of premorbid background in the formation of local infectious-inflammatory diseases is shown here. As can be seen from the figures (Figure 1), local infectious-inflammatory diseases are often caused by the influence of 2 or more factors of the premorbid background. In infants born as a result of physiological pregnancy (Group I), 93.7% had mild severity and 6.3% had moderate severity. No severe forms were found. In infants born as a result of pathological births and included in Group II, mild and moderate local infectious-inflammatory diseases were 55.4% and 27.8%, respectively. Among the infants included in Group V (in infants diagnosed with thymomegaly), the share of patients with mild scale was only 4% of the total number, and 84% were patients with severe scale.

Acute changes in cellular and humoral immunity, depending on the premorbid background, were found in infants suffering from local infectious-inflammatory diseases. Our studies prove that 31.3% of infants born as a result of a normal physiological pregnancy with local infectious-inflammatory diseases have moderate activation of cellular and humoral immunity. However, in infants included in Group II (born as a result of pathological pregnancies) in 22.2% of cases, a weakening of the cellular immune system was observed. Similar changes were observed in other groups.

In the next phase of the study, we studied the state of the immune system in infants with local infectious-inflammatory diseases depending on the type of nutrition. In breastfed infants (Group 1A), in 80-87% of cases, microbial-antigenic effects become the cause of activation of cellular-humoral immunity and non-specific factors of the body's defense. At the same time, in artificially fed infants with local infectious-inflammatory diseases (Group 1B), cell-humoral immunity decreased by 20 - 46%, and the

immune responses of neutrophil genesis decreased by 26.7 - 46.7%, respectively.

In infants of Group 2A, local infectious-inflammatory diseases developed on the basis of anemia and rickets. They showed a sharp weakening of the immune system, a significant decrease in the number of T-lymphocytes (CD4 + and CD14 + cells), as well as a weakening of the immunity of neutrophil genesis and moderate neutropenia. Infants included in Group III had anemia, malnutrition, and rickets as premorbid backgrounds. Their immune system functions were severely weakened. Immunoglobulin synthesis of CD-19 + cells (B-lymphocytes) is impaired as a result of a sharp decrease in the number of CD-4 + cells (i.e. T-helpers) in this group of infants. For this reason, IgA, IgM and IgG in the serum of patients from this group are low and below the norm.



Picture 1. Brief clinical characteristics of local infectious-inflammatory disesases in infants 6-12 years, depending on the nature of the premorbid background

They have neutropenia in 63% of cases and IgG change in 42% of cases. Thus, to study the relationship between the state of immune homeostasis in a sick infant and the severity of sepsis, the state of cellular and humoral immunity was determined in 15 infants with moderate sepsis and 20 infants with severe sepsis. Analysis of these immunological parameters and some indicators of non-specific immunity showed that in these infants, regardless of the severity of the septic process, there are accurate changes in all indicators of the immune system compared to healthy infants. These changes are

manifested by an increase in the number of CD + 8 T-suppressors and a decrease in other immunological parameters, CD3 + (T-lymphocytes), CD4 + (T-helpers), CD14 and CD16 cells, as well as the immune regulation index and LBTR (lymphocyte blast transformation reaction). Anemia was characterized by a decrease in the level of hemoglobin in the blood of 8 infants in the range of 90-100 g / l, and in 9 patients with a decrease in the range of 80-90 g / l. There were only 3 breastfed infants, and 14 artificially-fed infants aged from 1 to 2 months. Hereditary allergies were reported in 5 patients (29.4%) and in 7 patients (41.2%); ARVI had been recorded 1.5 to 2 months before admission. In addition to the above-mentioned improvements in cellular immunity in infants of Group I, there were also changes in the average mathematical quantities of humoral immunity. Thus, if the concentration of IgA, IgM, IgE in the blood serum increased with a high degree of accuracy ($p < 0.01$), then the amount of IgG decreased correctly ($p < 0.05$). Evidence for this is the tendency to increase the number of phenotypic CD14 + lymphocytes, which reflect the function of the monocyte-macrophage clause of immunity, and the presence of true neutrophilia in the blood in absolute and relative quantities of cellular immunity (in%). The results varied both in Group I and other groups.

The data show that the mathematical mean values of cellular immunity (CD3 +, CD4 + ITI, CD14 +, CD16 +, LBTR) in healthy infants were significantly reduced in comparison with the corresponding data ($p < 0.001$). The exception is CD8 + -suppressors, the quantity of which increases with high accuracy ($p < 0.001$).

In Group 2A patients, there was a highly accurate decrease in the amount of immune tolerance induction as a result of a decrease in CD4 + -helpers and an increase in CD8 + -suppressors. Due to this reversal, the value of the latter differed significantly from that of both healthy and sick infants in Subgroup 1B.

According to the average mathematical data, this decrease or increase in the parameters of cellular immunity in patients of Group 2A was not confirmed during the analysis of their individual

quantities. A comparative study of individual indicators of the immune system revealed that the frequency of deviations of one or another parameter of cellular immunity above or below the upper or lower limit of the norm is higher in patients of Group 2A than in infants of Subgroup 1A. Thus, if the individual values of ITI, LBTR and CD4 + -helpers were below the lower limit of the norm in 35.3%, 35.3% and 47.0%, of cases respectively, then there was no deviation in the individual levels of the parameters in patients with Subgroup 1B, i.e. their values were within the age limit. In Group 2A, the value of CD8 + -suppressors was above the upper limit of the norm in 41.2% of cases, as was observed in only 33.6% cases of Subgroup 1B.

Based on the results of a comparative analysis of individual indicators, it can be concluded that the high frequency and more expressed deviations in the parameters of cellular immunity in patients of Group 2A compared with infants of Subgroup 1B are due to aggravated premorbid background – rickets and anemia in Group 2A patients. The average mathematical values of humoral immunity IgA, IgM, IgE in patients of Group 2A are 2-3 times higher than in healthy infants ($p < 0.001$). As for the value of IgG and the amount of CD19 + (B-lymphocytes), their average mathematical values do not differ from the corresponding values in healthy infants ($p > 0.05$).Analysis of individual indicators of humoral immunity showed that in only 5 (29.4%) patients the serum IgA concentration was higher than the upper limit of age, and in 8 patients (47.0%) IgM was higher than the upper limit of age, in 5 patients (29.4%) IgG levels were below the lower limit of the norm. These data indicate a limited humoral immune response, and in most patients in Group 2A, its adequacy was observed in only 29.4% - 47.0% of cases. An increase in serum IgE above the upper limit of age was observed in 10 patients (58.8%), and the amount of disseminated intravascular coagulation (DIC) and their average molecular components was observed in 11 (64.1%) infants. Recent data confirm that the majority of infants in Group 2A have a high level of allergies and the possibility of developing allergic diseases in later life.

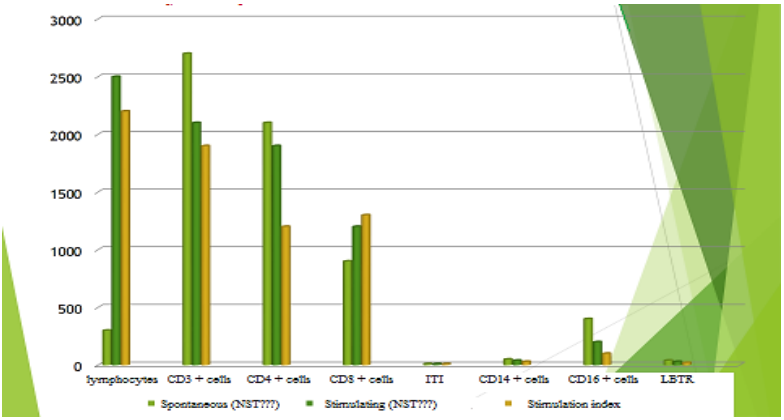
During the analysis of some indicators of non-specific protective factors of the body of patients of Group 2A, it was found that the absolute mathematical quantities of neutrophils in the peripheral blood, spontaneous and stimulating NST-test, stimulation index decreased to a high degree of accuracy compared to not only healthy infants, but also Subgroup 1B patients ($p < 0.001$).

Thus, the results of the study allow us to conclude that the microbial-antigenic effect of rickets in combination with anemia in Group 2A local infectious-inflammatory diseases patients with aggravated premorbid background leads to significant improvements in both cellular and humoral immunity and neutrophil ring parameters. In this case, rickets in combination with premorbid background and anemia has a significant effect on the degree of deviation in the immune system parameters. Evidence of this is the 1.5-2-fold increase in the frequency of inadequate response of infants of Group 2A to microbial-antigenic effects compared to the patients of Subgroup 1B. Moreover, if we judge the level of IgE and DIC mean molecular components in the blood serum of Group 2A patients, allergy is observed in 58.8 - 64.1% of cases. This, in turn, is one of the important factors in the development of expressed immunodeficiency in such patients. It should be noted that the deviation of these or other parameters from the lower or upper limit of the age limit in 35.3 - 47.0% of cases of cellular immunity, 29.4 - 47.0% of cases of humoral immunity, and 35.3-58.8% of cases of non-specific protection factors were observed.Subfractions IgG - IgG1, IgG2, IgG3, IgG4 are actively involved in the formation of immunological reactions in the body. IgG1 and IgG3 subfractions accelerate the opsonization of bacteria and increase the facsimile activity of macrophages and neutrophils. IgG2 and IgG4 subfractions consist of polysaccharide antibodies of bacteria. As can be seen in the slide, IgG3 and IgG4 subfractions decreased in infants aged 6 to 12 months with local infectious-inflammatory diseases.Humoral immunity in infants with local infectious-inflammatory diseases was studied depending on the aggravated premorbid background. In this case, changes in the amount of immunoglobulins were detected.

Thus, for example, the amount of IgG is 1.5 times lower than normal. Apparently, this is due to the effect of bacterial factors on the process of cell differentiation CD4 + (helper) and CD + 8 (suppressor).Subfractions IgG - IgG1, IgG2, IgG3, IgG4 are actively involved in the formation of immunological reactions in the body. IgG1 and IgG3 subfractions accelerate the opsonization of bacteria and increase the facsimile activity of macrophages and neutrophils. IgG2 and IgG4 subfractions consist of polysaccharide antibodies of bacteria. As can be seen in the slide, IgG3 and IgG4 subfractions decreased in infants aged 6 to 12 months with LIX.The results of a study of serum IFN - α levels in the blood showed that in the early neonatal period in Subgroup 1.1, IL-8 level was 2.7 times higher than in the control group and 1.8 times higher than in Subgroup 1.2. A direct correlation was found between IL-8 levels and viral load levels. Decreased levels of IL-12 in newborns in Group II lead to a violation of the relationship between non-specific protective and specific immune mechanisms compared to the control group. IL-4 levels in infants in Subgroup 1.1 and Group II were 3.6 and 4.0 times higher, respectively, than in the control group, reflecting the predominance of anti-inflammatory cytokines and leading to a decrease in anti-infective protection. Only in the 3rd month of life did IFN - α levels increase. IL-4, IL-6 levels decreased. In Subgroup 1.2, IFN-α values increased significantly in 1 month compared to the early neonatal period, and IL-8 and IL-6 decreased. Besides, IFN -γ increased progressively over 3 months.The nature and direction of improvements in the parameters of humoral immunity in infants of Group IV were the same as in patients of Group II. Group IV also showed a 2-fold increase in IgA, a 2.1-fold increase in IgM, a 4.1-fold increase in IgE, and a 4.6-fold increase in DIC in blood serum and a 0.3-fold decrease in IgG ($p < 0.001$) in healthy infants.

At the next stage in the study of the role of IgG subclasses in the pathogenetic mechanisms of development of local infectious-inflammatory diseases and sepsis, we were interested in the following issue. Analysis of the data shows that the improvement in the average mathematical concentration of total IgG and its

subclasses (IgG 1, IgG2, IgG3, IgG4) in the serum is unidirectional, and the high accuracy of their reduction is not limited to healthy infants (p <0.001), but also to patients of Groups 1A and 1B, as well as to infants of Group 2A (p <0.001). In both these and previous groups, there is some interest in comparing the individual quantities of IgG and its subclasses in the serum with the clinical signs of the disease. The role of the premorbid background on the basis of local infectious-inflammatory diseases was given here. Local infectious-inflammatory diseases are often caused by 2 or more factors of the premorbid background. In infants born as a result of physiological pregnancy (Group I) in 93.7% of cases local infectious-inflammatory disease was mild, in 6.3% of cases it was moderate. No severe forms were found.



Picture 2. The state of cellular immunity depending on the severety of sepsis in infants

Acute changes in cellular and humoral immunity, depending on the premorbid background, were found in infants suffering from local infectious-inflammatory diseases. Our researches confirm that 31.3% of infants with local infectious-inflammatory diseases born as a result of normal physiological pregnancy have moderate activation of cellular and humoral immunity. However, in infants included in Group II (born as a result of pathological birth) in 22.2% of cases, a weakening of the cellular immune system was found. Similar

changes were also observed in other groups. For example, local infectious-inflammatory diseases were particularly acute in infants with thymomegaly and dysbacteriosis.

In the next phase of the study, the state of the immune system in infants suffering from local infectious-inflammatory diseases was studied depending on the type of their nutrition. In infants who are naturally breastfed (Group 1A), microbial-antigenic effects in 80-87% of cases turn into the reason of cell-humoral immunity and non-specific protective factors of the organism. In artificially-fed infants with local infectious-inflammatory diseases in Group B (Group 1B), cell-humoral immunity decreased by 20 - 46%, and immune responses of neutrophil genesis decreased by 26.7 - 46.7%.In infants of Group 2A, local infectious-inflammatory diseases developed on the basis of anemia and rickets. They noted a sharp weakening of the immune system, a significant decrease in the number of T-lymphocytes (CD4 + and CD14 + cells), as well as a weakening of the immunity of neutrophil genesis and moderate neutropenia.The infants included in Group III had anemia, malnutrition, and rickets as premorbid backgrounds. Their immune system functions were severely weakened. In infants in this group, the synthesis of immunoglobulins by CD-19 + cells (B-lymphocytes) is impaired as a result of a decrease in the number of CD-4 + cells (i.e. T-helpers). For this reason, IgA, IgM and IgG in the blood serum of patients from this group are reduced and found below the norm. Neutropenia is observed in 63% of cases, and IgG change is observed in 42% of cases.Analysis of the immunological parameters of each patient revealed that in the moderate scale of sepsis, the parameters of cellular immunity were below the minimum in 34-67% of cases, and in its severe form in 45-85% of cases.

Humoral immunity was studied in infants with local infectious-inflammatory diseases depending on the aggravated premorbid background. In this case, changes in the amount of immunoglobulins were detected. Thus, for example, the amount of IgG decreased by 1.5 times compared to the norm. Apparently, this is due to the influence of bacterial factors on the process of

differentiation of CD4 + (helper) and CD + 8 (suppressor) cells.IgG - IgG1, IgG2, IgG3, IgG4 subfractions are actively involved in the formation of immunological reactions in the body. IgG1 and IgG3 subfractions accelerate the opsonization of bacteria and increase the facsimile activity of macrophages and neutrophils. IgG2 and IgG4 subfractions consist of polysaccharide antibodies of bacteria. As seen in the slide, IgG3 and IgG4 subfraction levels decreased in infants aged 6 to 12 months with local infectious-inflammatory diseases.

Therefore, the data show that the improvements in the blood serum concentrations of total IgG and its subclasses in patients with severe sepsis are unidirectional, and their mean mathematical parameters are significantly reduced compared to the relevant data in healthy infants. When comparing the degree of individual improvement in the concentration of total IgG and its subclasses in sick infants, it was found that the quantities of subclasses are more variable than the total IgG level.

RESULTS:

1. Socio-biological factors have a negative impact on the nature of local infectious-inflammatory diseases and sepsis in infants (type of nutrition, pregnancy complications, CNS hypoxia, thymomegaly, dysbacteriosis, hypotrophy, rickets, anemia, acute respiratory viral infection).
2. The severity of local infectious-inflammatory diseases depends on the presence or absence of the above premorbid conditions.
3. In infants born as a result of physiological pregnancy and fed naturally, local infectious-inflammatory diseases were mild in 93.7% of cases.
4. 55.4% of infants born as a result of pathological births and fed artificially had a severe form of local infectious-inflammatory diseases. In infants with premorbid background and concomitant thymomegaly and dysbacteriosis, severe forms of local infectious-inflammatory diseases were found in 84.0% and 82.2% of cases, respectively.
5. The amount of lipid and small-mass molecules (SMM) peroxidation products of the immune system in infants plays an

important role in the mechanism of pathogenesis of local infectious-inflammatory diseases and sepsis. There is a certain correlation between changes in these indicators and the characteristics of the clinical course of the disease. The nature of the premorbid background is of great importance in this interaction.

6. Immunological parameters play an important role in the development of local infectious-inflammatory diseases and sepsis in infants. Reliable criteria in this case may be immune parameters. Early criteria for the mild course of sepsis may be an increase in serum IgG concentration in the observed dynamics.

PRACTICAL SIGNIFICANCE

Based on the analysis of laboratory data, it was determined that a main position in the development of local infectious-inflammatory diseases and sepsis is held by the degree of expression of allergens in the body. Immune parameters (CD4 +, CD16 +, LBTR, IgG2, IgG4) can be considered as accurate criteria for determining the dynamics of the pathological process to clarify the diagnosis of sepsis in infants, to predict the transformation of local infectious-inflammatory diseases into sepsis, and to determine the possible consequences of the disease (recovery, complication and death).

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