Research Article

ASSOCIATION OF IMMUNOLOGICAL, LABORATORY AND CLINICAL STATUS AT NORM AND PATHOLOGY

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ABSTRACT

We studied the strong correlation (coefficient>0.6) with a variety of clinical and laboratory parameters in patients as an additional tool for the analysis of the integrating function of the immune system. Education index were evaluated between intra-(immune), inter-system (immune, biochemical, and others.) And non-system (immune and clinical) bonds in immuno-neuro-endocrine, in-infectious, somatic and others pathologies. The work is aimed at clarifying the organisms regulate immune system function in different types of pathology and therapy, including immunotropic, the establishment of key targets and indications for the choice of efficient products

INTRODUCTION

The development of medicine from simple to complex led to the differentiation of clinical disciplines and equally complex laboratory examination of patients. As a result, narrowly specialized professionals have appeared often not even finding a common language among themselves and, most importantly, with a certain loss of the systemic pathophysiological idea of the origin and course of pathology in general (Zemskov *et al.,* 2007).

It isobvious, this state of affairs is reflected in the formulation of the principles of treatment of various diseases. One of the ways toobjectively evaluate the regulatory mechanisms of homeostasis in general and the immunological one in particular is the use of correlation analysis. At the same time, the unambiguous interpretation of the presence and the number of reliable links between the indicators of laboratory or any other status has not been finally determined. There is an opinion that the more correlative links between parameters, the more the system is tense (Lebedev, Ponyakina, 1997). There is also an oppositepointof view (Zemskov *et al.,* 2013). At the same time, the established fact is the increase in the number of correlations between immune laboratory indicators in the stage of clinical remissafter treatment. Thus, this method is an indirect criterion

for evaluating the effectiveness of therapeutic effects. Simultaneously, the qualitative analysis of the associated parameters makes it possible to reveal intimate mechanisms of variations in the laboratory sphere during the development of the disease, the implementation of immunocorrection, etc. (Zemskov *et al.,* 2013).

Association of immune and laboratory status in healthy persons

It has been established that the components of the immune laboratory status form a certain matrix of integrative connections in healthy individuals - healthy disposable blood donors. In this case, the populations and subpopulations of lymphocytes have a direct correlation with the level of common lymphocytes, which seems quite logical and natural without any discussion. On the other hand, the lymphocytes with the markers CD3+, CD4+, CD19+ were positively associated with the stab neutrophils. At the same time, the phagocytic number, PN, (the test for the absorption capacity of phagocytes) had a negative dependence on the rod nuclear cells.

The relationship between segmented leukocytes and lymphocytes, mainly related to the T-link of immunity, turned out to be rather complicated. So, CD3+, CD4+, CD19+ cells

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(common T-lymphocytes, T-helpers and B-cells) had a positive dependence on this type of white blood cells. These data suggest that, apparently, the expression of different receptors, even in the same populations of lymphoid cells, affects their ratio with thestab neutrophils. Reliable connections of populations of lymphoid cells with the level of basophils and eosinophils involved in the implementation of allergic reactions were lesssignificant. Lymphocytes with the CD3 + marker had a negative dependence on basophils, CD4+ - oneosinophils (Eo), and the phagocytic number had the positive one from the same cells (Zemskov *et al*., 2007; 2016).

The presented data indicate a significant association of constituent immune and hemograms determined by the set of receptors on the membranes of the cells under the analysis belonging to different stems of hematopoiesis. It is not excluded that the observed regularities may have a certain practical significancein the future. For example, a directed increase in the level of T-cells and T-helpers will cause a decrease in the level of basophils and eosinophils, and suppression of the absorbing activity of leukocytes will lead to stimulation of the number of rod nuclear cells. The most pronounced correlation between biochemical parameters and stabneutrophils has been documented. The content of cholesterol, total and free bilirubin, thymol test and blood amylase level had a positive relationship with the pool of stab nucleated leukocytes, and the antioxidant activity of plasma was inversely correlated with the number of those cells. With reference to the content of segmented cells, the similar regularity was recorded towards the total bilirubin level, thymol test, ALT (alanine aminotransferase), prothrombin and to the total protein concentration. In other words, the liver function, evaluated by various reactions, directly "correlated" with the number of granulocyte leukocytes.

Monocytes were found to have other patterns. AST (aspartate aminotransferase) and diene conjugates had a negative, and on the contrary, antioxidant activity of plasma and catalase had a positive relationship with these cells. Associations with the number of common lymphocytes and basophils were of less significance. Some associations of biochemical parameters with the T-link of immunity were revealed, positive correlations undoubtedly prevailed over negative ones. At the same time, the level of common T-lymphocytes had positive correlations with thymol test, blood amylase, cholesterol, prothrombin levels, antioxidant activity of blood plasma, superoxide dismutase activity, and the negative ones-with ALT. Tcytotoxic, respectively, had the samecorrelation with common and free bilirubin, thymol test, blood amylase, glucose and ALT.T-helpers (Th) - with thymol test, prothrombin, antioxidant activity of plasma and superoxide dismutase. All three types of cells had a negative, reliable relationship with ALT.

Killer lymphocytes were "dependent" on the antioxidant activity of plasma and superoxide dismutase (SOD) level. The level of total and unconjugated bilirubin, prothrombin, antioxidant activity of plasma and superoxide dismutase levels were positively related to the number of B cells. The associations of immune globulins proved to be of little significance in this respect, which is explained by the fact that these proteins are derived from the content of B cells and are subject to considerable variation from a number of reasons.

Absorptive capacity of leukocytes, estimated by phagocytic index (PI) and phagocytic number (PN), was under the "negative control" - prothrombin, ALT, thymol test, free and bound bilirubin and under the positive one - from the level of cholesterol. Prothrombin appeared to be negatively associated with the metabolic activity of neutrophils, while the total bilirubin, AST and total protein level were positively associated with it. In general, it should be recognized that a highly reliable, mainly positive, dependence of the level of functioning of the hepatobiliary system, certain lipid metabolism parameters and parameters of lipid peroxidation on granulocyte content and the carriage of differentiation markers on membranes of lymphoid cells, especially T-dependent ones, is found in healthy individuals. There are regularities in terms of the association of absorbing and metabolic activity of phagocytes with the biochemical status (Zemskov *et al*., 2013).

Association of parameters of immunelaboratory status in various diseases

Meningitis in children

In patients with this pathology, T-lymphocytes were positively "dependent" on the content of leukocytes, segmented nuclear cells, monocytes and ALT; regulatory subpopulations with helper and suppressor properties were respectively dependent on T-cells, leukocytes and ALT; B-cells - on albumin; phagocytic index – on ALT; phagocytic number - on α-1 and β-fractions; active nitroblue tetrazolium (NBT) test - on spontaneous NBT-test (Kuprina, 1999).

Bronchopulmonary diseases

Conducting the correlation analysis of the results of the biochemical examination of patients with COPD (chronic obstructive pulmonary disease) revealed an inverse relationship of the SOD enzyme with the components of the lipid peroxidation-antioxidant defense (LPO-AOD) system, with the products of LPO-MDA (lipid peroxidation -malonic dialdehyde) and hydroperoxides (HP), with the total serum lipids acting in this case as antioxidants and with MWM (medium-weight molecules). On the other hand, there is a direct correlation between the content of MWM and LPO products, hence the MWM acts as an agent that aggravates the toxic effect of activated LPO. Also, in COPD a positive correlation was found between the level of lipid peroxidation product - MDA and the duration of the disease, and, likewise, the negative one was discovered between the endogenous antioxidant enzyme SOD and the severity and duration of the pathology. It was also established that the content of T-cells, T-cytotoxic and T-helpers, is in inverse correlation dependence on the level of products of LPO and CIC (circulating immune complexes), which can be explained by the immunosuppressive effect of LPO on the immune system, mainly on its cellular unit.

Factorial analysis confirmed the inhibitory effect on the T-link of the immunity of LPO-MDA and HP products, the toxic one-on the MWM, to lesser extent - on CIC. A similar pattern of the relationship of LPO-AOD, as well as the level of biogenic amines was found in patients with endogenous bronchial asthma. At the same time, certain relationships were found between the indicators of the LPO-AOD system with the level of biogenic amines - inverse correlation relationships between

the parameters of the LPO-AOD systems and biogenic amines, serotonin and antioxidants, and positive relations of LPO products with histamine and serotonin (Bolotskikh, 2007; Zemskov *et al.*, 2013).

Viral infections

When carrying HBsAg, it was found that the lymphocytes andstab neutrophils had a positive correlation with T-cells and IgM. Segmented leukocytesand eosinophils appeared to be negatively associated with T-cells, IgG, and the latter positively with the number of null-cells without T- B- cell markers, constituting an immature reserve of highly differentiated and killer lymphocytes. The level of monocytes positively correlated with the content ofT-helpers, Tcytotoxic, zero cells, and the value of PN. At the same time, the content of lymphocytes positively «depended» on the level of cholesterol in viral carriers, the stab cells depended on total bilirubin, hemoglobin - on free bilirubin, and eosinophils – on ALT. HBsAg carriers did not have reliable connections with the main populations and subpopulations of cells and, in the first place, T-cells. A positive association was recorded between the total protein concentration with IgM and IgA levels, and free bilirubin level was positively associated with the absorption capacity of phagocytes, whereasglucose concentration was with this function of phagocytes in a negative connection (Pritulina, 2007).

Multiplesclerosis

In the acute stage of multiple sclerosis segmented leukocytes and monocytes it turned-were positively associated with the bound bilirubin and lipoproteins, and stab cells associated with bilirubin. Components of the cellular immune system - T-cells, NK-cells and HLA-DR+ lymphocytes tested positive association with lipoproteins and CD16+natural killereven with total bilirubin. B-cells "were" positive "dependence" of associated bilirubin, and the level of immune globulin class A - negative dependence on lipoproteins. As for the functional activity of phagocytic level, determined by the absorbing activity and oxygen metabolism, it was found that the first functionwas mathematically negative "dependent" on the concentration of lipoproteins and associated bilirubin, and second, respectively, of diene conjugates. But this function was positively associated with the bound bilirubin and lipoproteines. In other words, lipid metabolism and associated bilirubin, apparently, "influence" on oxygen metabolism of neutrophils.

In the stage of remission of multiple sclerosis the main regulatory subpopulations of T cells, as well as of the HLA-DR+ lymphocytes, have a reliable positive correlation with lymphocytes. Positive dependence of T-helpers was associate on the concentration of kettodins, HLA-DR+ lymphocytes – with glutathione peroxidase activity, B lymphocytes - on catalase activity, metabolic ability of phagocytes - on peroxide resistance of red blood cells. The stab granulocytes have a negative dependence on the level of B-lymphocytes, T-cells, T-helpers, Tcytotoxic, and the positive one -on the absorption capacity of phagocytes. Monocytes were found to be associated with T cells, IgM and CIC. Stab-nucleated white blood cells formed reliable correlation links with thymol test and glucose, and monocytes did the negative ones with Schiff bases. The analysis of qualitative associations revealed that significant

correlations between the components of hemo-immunograms with tests characterizing the functional state of the liver and lipid metabolism (free and associated bilirubin, thymol test, lipoproteins) were recorded in patients at the stage of exacerbation of the disease. In patients in the remission phase, associations are already formed with parameters of lipid peroxidation and antioxidant protection, minimal blood lipids (Lutsky *et al.*, 2012).

Cerebrovasculardiseases

When determining the integrative activity of key parameters, measured by the number of formed links of immunological and other studied indicators, it was found that in uncomplicated hypertension (arterial hypertension, AH 1), the total number of significant associations was 22, including mainly immunological tests and AOD(antioxidant defense) factors. The second and third stages of arterial hypertension (AH 2, AH3) led to the formation of a total of 30 interdependencies, while maintaining the same pattern. At a hypertensive crisis (HC) the picture has changed. The total number of connections increased to 35. At the same time, the orientation of the dynamics was approximately evenly distributed among immunological tests, LPO products, AOD factors. This, apparently, indicates that the hypertensive crisis for this type of analysis is significant differ from hypertensive disease regardless of the stage of the disease. A new quality was established in patients with acute hypertensive encephalopathy (AHE).Against the background of the general increase in the number of associations - 40, the most important were the links of immunological parameters with the factors of the antioxidant system and lipid peroxidation. In this case, the formation of intrasystemic links of immune resistance factors among themturned out not to be pathognomonic.

In transient ischemic attack (TIA) with the same number of correlation links - 40, their distribution by decreasing severity turned out to be different. Initially, the immunological intrasystemic took place, then hematologicalPOL products, and, to a lesser extent, the elements of antioxidant mechanisms. Ischemic insult (II) also caused the formation of 40 dependencies.

However, the greatest stress was observed in the LPO-AOD systems, with the integration of the immuno-hematological parameters in the background. With hemorrhagic insult (HI), the total number of connections dropped to 31 with the clear advantage of the integration of immuno-metabolic processes. Thus, the general pattern of integrative activity of key components of the immuno-laboratory status in cerebrovascular diseases is the progressive increase in the number of correlation links from the normal level as the pathology worsens, with the exception of hemorrhagic insult, in which the quantitative growth of correlation links was not so significant.

This is may be accompanied by the predominant involvement in the pathogenesis of cerebrovascular diseases in the parameters of lipid peroxidation and, especially, the antioxidant system in case of severe outcomes of these diseases and the phenomenon of association of the dynamics of immunological indices of antioxidant system factors and free radical oxidation of lipids and proteins, with the severity of the pathological process. The proof of this is the rating of correlation links with AOD: HI→ II→ TIA→AH-3→ AH-2→ AH-1; and with FRO

(freer radical oxidation): HI → II → TIA → AHE→HC →AH-3 → AH-2 иAH-1 (Lutsky *et al*., 2012).

Diabetes mellitus

The components of the T-dependent immunity unit and the HLA-DR+ lymphocytes formed a strong positive relationship with the level of lymphocytes, which seems quite natural, since the latter essentially represent the totality of lymphoid elements. At the same time, the content of the two main regulatory subpopulations and HLA-DR+ lymphocytes had a negative dependence on segmented leukocytes and monocytes, and the level of common T cells was from basophils andstab stemcells. The indices of oxygen metabolic activity and absorption capacity of phagocytes proved to be associated positively and negatively with the level of the same cells; the production of IgG and A was positively correlated with the number of segmented leukocytes, and the concentration of IgG and M was negative with the number of lymphocytes and eosinophils. These data to some extent indicate, firstly, that the constituents of the hemo- and immunograms are closely related, and secondly, that the regulatory lymphoid cells with helper and suppressor properties are contained in the antiphase with segmented-nucleated leukocytes, while the main characteristics of phagocytic cells are differently correlated with basophils and stab cells. In addition, a predominant positive dependence of metabolic parameters on the content of white blood cells was revealed.

The most demonstrative links are established in basophils with cholesterol, lipoprotein, glutathione peroxidase activity, glutathione reductase and peroxide resistance. Approximately the same set of dependencies was also in stab cells. The content of total and associated bilirubin were positively related to the number of erythrocytes and the concentration of hemoglobin. The associations of eosinophils and segmented leukocytes were much weaker. In the first case, the dependence on the total protein and thiols was recorded, in the second case it depended on urea and blood amylase. At the same time, the activity of superoxide dismutase was positively related to the level of B-cells, the thymol test - with IgM concentration, and the diene conjugates, associated and total bilirubin had a reliable but negative association with the level of this protein.Quite a variety of correlations were documented when evaluating the absorption and oxygen metabolic capacity of phagocytes. Thus, phagocytosis itself was positively associated with malonic dialdehyde and negatively with peroxide resistance, glutathione peroxidase activity, common thiols, lipoproteins, cholesterol, and oxygen metabolism of these cells was positively associated with antioxidant plasma activity (Meshcheryakova, 1999).

The connection of immune laboratory and clinical indicators with the degree of resistance of children who undergone severe asphyxia

When performing the correlation analysis in children, the direct correlation was found between the phagocytic number in the cord blood and the long anhydrous interval in the mother with the correlation coefficient. The inverse relationship has been revealed between gestosis and level of CD95+ lymphocytes, NBTact in the umbilical cord blood. A positive correlation was noted between the presence of gestosis in the mother and the content of CD8+ lymphocytesin the umbilical cord blood. Multidirectional relationships were determined between the

concentration of IgG on the 5th day and respiratory distress, the duration of the "ventilation", gestosis, acute renal failure in newborns, the duration of jaundice. In addition, there was a unidirectional direct correlation between the level of CD95+lymphocyteson day 4-5 and polyhydramnios, between the number of CD56+lymphocyteson day 4-5 and the perinatal CNS (central nervous system) lesion. The conducted correlation analysis revealed a negative relationship between the NBT active in the umbilical cord blood and malignancy, between the level of CD4+lymphocyteson days 4-5 and polyhydramnios, vaginal candidiasis in the mother during pregnancyendometritis. A negative correlation between the level of IgG in the umbilical cord blood and herpes viral infection in the mother during pregnancy was also detected. As a result of this analysis, taking into account the above-mentioned interrelations, it can be assumed that the physiological and gynecological pathology of the mother, as well as the complicated course of pregnancy, affect the formation of the immune status of the newborn.

The influence of the immune status on the degree of resistance in children who undergone severe asphyxia was also established. For example, at birth in children there is a statistically significant negative relationship between the levels of CD3+, CD4+, CD8+, CD95+lymphocytes and the degree of resistance, i.e, with an increase in the number of these cells, the index of acute diseases was low. It was revealed that the level of IgA in the cord blood correlated with the subsequent formation of atopic dermatitis in the child, anemia, CD56+ lymphocytes - with intestinal disbiosis, urinary tract infection, vulvovaginitis. The revealed interrelations between immune parameters and the degree of anti-infective resistancein children under 1 year confirm that the brevity depends on the immunological reactivity of children who undergone severe asphyxia and the complications of pregnancy with the mother (Bugrim, 2011).

Association of indices of the immuno-laboratory status in the treatment of mono diseases

To assess the stated pattern in patients, the key parameters of the immune system disorders were determined before and after differential treatment, with an assessment of their ability to form strong correlation links with the terms of the laboratory status.   In the acute period of deep pyoderma, the ability of key parameters of the immune system disorders formula to form strong bonds with immune globulins of class G, B-cells, neutrophils, absorbing and metabolic ability of phagocytes was established. After traditional treatment, the terms of the (FISD) (formula of immune system disorders) appeared to be associated with the dynamics of T-B-cells, regulatory subpopulations, IgM, leukocytes and lymphocytes.   With additional use of *ozonized sodium chloride*in the treatment of patients, the number of harmoniously changing laboratory parameters included: B-cells, PI, PN, IgA, IL-6, leukocytes, lymphocytes. Metabolic and antioxidant *hypoxen* (*antihypoxant and antioxidant Polydihydroxyphenylenethio-sulfonate sodium*), in turn, modified the correlation processes in the laboratory sphere, having changed the set of correlatively related parameters-Tcytotoxic, IgM and G, PI,IL-8, leukocytes, lymphocytes. Combined   pharmaco-non-medicamentous modulation of patients with PSTI (purulent soft tissue infection) provided a significant association of regulatory T-

cells, B-lymphocytes, main classes of Ig, NBT$_{spont.}$, leukocytes, lymphocytes (Zemskov *et al.*, 2016).

With purulent softt issue infection (PSTI)

The key terms of the original FISD in the acute period of the disease formed the following correlations: Tcytotoxic cells were positively associated with leukocytes; eosinophils - negatively with lymphocytes; B-cells are also positive with IgG and T-helpers. There is a significant simplification and changes in the nature of the association of the components of the immuno-laboratory status under the influence of the pathological process. In patients with PSTI after the implementation of the basic treatment without modulators, the key parameters of the final formula of immune system disorders were positively related, respectively: CD8+lymphocytes - with IgM, common lymphocytes, leukocytes; neutrophils - with monocytes, CIC - with T-helpers; In this way6 strong correlations were formed. With the additional inclusion of *derinat(officinal preparation of high molecular DNA)* in traditional treatment, the nature of the associative processes of key laboratory indicators has changed. Cytotoxic cells were associated with lymphocytes, neutrophils, monocytes, phagocytic index, IgG. Monocytes coordinated with leukocytes, neutrophils, eosinophils, T-cytotoxic/suppressors.

Carrying out of the combined correction of patients with *lycopide* (*bacterial muramyl dipeptide preparation*) and *derinat* led to the variation of the final FISD, a quantitative and qualitative change in the formation of the correlation bonds of its terms. Thus, key tests (CD8$^-_2$IL-8$^+_2$CD19$^-_2$) formed strong correlation links with - leukocytes, lymphocytes, T-helpers, with T-cells, IgG. In women with acute salpingo-oophoritis (ASO), the terms of the original FISD-Eo$^+_3$IgM$^+_3$IL-6$^+_3$ formed six strong positive associations with leukocytes, neutrophils, TNF-α, Tcytotoxic, MWM, IgG (Zemskov *et al.*, 2013).

Acute inflammation of the uterine appendages

Conducting the traditional treatment of acute inflammation of the uterine appendages led to the change in the set of diagnostic tests in the FISD and the spectrum of parameters involved in the correlation. These tests - IgM$^+_3$IgA$^+_3$CIC$^+_3$ positively depended on the level of leukocytes, lymphocytes, TNF-α, B-cells, negatively - on the content of NK, T-helpers, of the main classIg, the magnitude of PI. Additional prescribing of *immunomax* (*immunomodulator Acid peptidoglycan with a molecular weight of 1000-40000 kD*) to patients slightly increased the number of correlations - the components of FISD-CD11b$^+_3$IL-6$^+_3$IgM$^+_3$ were associated with PN, HBTsp, lymphocytes, T-cells, TNF-α,MWM, neutrophils, IgM and IgG. Introduction of patients with ASO *tamerite (antioxidant, immunomodulator, anti-inflammatory drug- Aminodihydroph - thalasindione sodium)* contributed to the association of IL-8,IL-4, Th, phagocytes, HBTac, IgG and IgM, T-B-cells, MWM, lymphocytes, monocytes, and eosinophils. The key targets of kipferon-Eo$^+_3$IL-6$^+_3$IgG$^+_3$ in the treated women with ASO were correlated with the level 9 of hemato-immunological parameters (Gridina, 2005).

Exacerbation of chronic salpingo-oophoritis

In patients with exacerbation of chronic salpingo-oophoritis, the key indicators of FISD before treatment formed six strong, in all cases, positive connections, respectively - with leukocytes, neutrophils, CIC, Tcytotoxic, IgG, TNF-α. In the same patients after traditional treatment at discharge from the hospital, the diagnosis of significant components of the final formula of immune system disorders revealed the formation of already 9 strong bonds, five positive, four negative, 7 inside, 2 - non-systemic. In the case when *imunofan (synthetic thymomimetic)* was included in the therapeutic complex, the components of the final FISD have changed the spectrum of associations. Regulatory T-subpopulations were positively associated with each other and negatively - with IgG, in healthy individuals the same index was associated with lymphocytes, neutrophils, IgM with positive and T cells with negative sign. NK changed in sick women negative associated with IgM, the number of phagocytes, PI and in the "control" group they were positive associated with CD11b+lymphocytes, IgA and CIC. IL-8 levels were positively associated with leukocytes, eosinophils, and negatively associated with IgG, IL-4.Simultaneously it positively "bound" to IgM and α-TNF and negatively to Th, PI, PN. Under similar conditions, the *KIPferone (complex immunoglobulin preparation)* also cause emergence of positively associations of IgG ,with PI, CIC, MWM, but the concentration of IL-6 was negatively correlated with the level of Tcytotoxic, positively - with neutrophilic leukocytes, anti-inflammatory IL-4. PN formed a positive association with PI. *Gepon (immunomodulator, antiviral-Treonyl-glutamyl-lysyl-lysyl-glutamyl-arginyl-arginyl-glutamyl-treonyl-valyl-glutamyl-arginyl-glutamyl-lysyl-glutamate)*in its turn, modified the nature of immuno-dependent variations in the women with purulent-inflammatory diseases of the reproductive organs.In patients among the associated parameters were leukocytes, B-cells, T-h, IgM, eosinophils, circulating immune complexes, peripheral phagocytes. In patients subjected to a three-component combination modulation of *imunofan,KIPferone*and *gepon* simultaneously, the qualitative spectrum of parameters with the coordinated dynamics of the terms of the immune system disorders included: immune globulins of class A, circulating immune complexes, phagocytic index and number, spontaneous NBT test,medium-weight molecules, interleukin-8, leukocytes, neutrophils.

In acute pyelonephritis, the terms of the initial formula of immune system disorders formed strong links only with activated NBT-test and B-cells. After traditional treatment, their number increased to – T-cells, T-h, IgG, PN. After modulation with *lycopid*, the number of associated parameters included IgM, CIC, NBTsp, PI, erythrocytes, segmented nuclear cells, ESR (erythrocyte sedimentation rate); also with *ridostin*(*officinal high molecular weight RNA*)- T-cells, their regulatory subpopulations, Ig of three classes, PI, leukocytes; also with combinations of *lycopid* with *ridostin*– B-cells, T-h, Tcytotoxic, IgG, IgA, IgM, leukocytes, lymphocytes (Butyrina, 2005).

Urogenital chlamydiosis

Three diagnostically significant tests revealed in patients with exacerbation of urogenital chlamydiosis before treatment:

$IgM^+_3NBTact^-_2CD3^-_2$ formed totally5 positive links, respectively with – B-cells, T-h, phagocytes, lymphocytes and NK. After non-immunotropic treatment, the key parameters - immature granulocytes - were positively related to the level of segmented-nuclear cells; T-lymphocytes - respectively to T-h and lymphocytes; IgG to IgM, T-h. In sum, diagnostically significant indices led to strong correlations in 6 cases, in five - with a positive sign. The combination of the basic treatment with the *neovir* (*immunomodulator Cridanimod*) contributed to the coordinated dynamics of key indicators in patients with urogenital chlamydia with 6 indicators. Eosinophils were positively associated with immature and mature granulocytes. NK, respectively, with T-lymphocytes. TNF-α is also positively connected with the proinflammatory cytokine IL-6. Additional inclusion of *hypoxen* in the treatment complex contributed to the modification of the final FISD $CD16^+_3IgM^+_3CD11b^+_3$ and revealed the formation of strong correlations with the main class of Ig, leukocytes, NK cells, lymphocytes, in total in 6 cases. In the acute period of herpetic keratitis, the associative activity of the initial FISD tests was low and included only two names – T-h and lymphocytes. Conducting traditional treatment of the disease completely eliminated the integration ability of the components of the final FISD. After using metabolic *cigapan (adaptogenic, antioxidant, immunomodulating and reparative action of powder of horns of reindeer)* in the treatment of patients, NBTsp and leukocytes entered the integration; also after using *derinat*– T-h, Tcytotoxic, leukocytes and lymphocytes; and after using *cygapan* with *derinat*-T-Bcells, Igoftwo classes, NBTsp, leukocytes, lymphocytes (Zemskov et al., 2013).

Association of indices of immuno-laboratory status in the treatment of a combination of diseases

Combination of chronic autoimmune thyroiditis (CAIT) with chronic obstructive pulmonary disease (COPD)

In healthy volunteers from the comparison group, the three key parameters of the FISD formed a total of 17 links, mainly with immunological indicators - the main populations and subpopulations of lymphocytes, IgG and IgM, CIC, and some phagocytic and hematological parameters. In patients with CAIT, the number of correlations sharply fell to 5. Thus, TAT (autoantibodies to thyroglobulin) was positively associated with the CIC; IgG with IgM, IgA, CD19+, CD8+, CD4+ lymphocytes. At COPD, 6 strong associations were established, which is indirectly indicated by a similar decrease in stress in the immune-laboratory sphere, as in the previous case in quantitative terms.

However, at the same time, qualitative variations of interrelations also occurred, mainly intra-systemic correlations between immunological tests - CD4+, CD8+, IgM, CIC, MSM, NBT$_{act.}$ Combined pathology (CAIT + COPD) caused the decrease in the number of correlation links. Natural killers formed the positive relationship with monocytes, CIC - with B cells. It seems that the severity of the combined disease leads to a more substantial simplification of integrative processes in the laboratory sphere. In patients with CAIT after baseline treatment, the terms of FISD formed dependencies with IgG, NK, Tc, T-h, CIC, TNF, and lymphocytes. In patients with COPD, the total number of strong bonds was 6.The three leading indicators, generalized in FISD, were associated with

the level of NK, mature granulocytes, T-h, the value of NBTsp, IgG, TNF-α. The set of key test targets in patients suffering from a combination of diseases treated with conventional therapy with the inclusion of *L-thyroxin* formed strong links with the following parameters: PI coincided with the variations in PN, IgM, IgG; anti-inflammatory cytokine IL-6. In turn, IL-6 was associated with T-h, PI, PN. The complex therapy of patients with CAIT with *L-thyroxine* and *derinate* facilitated the formation of strong links with 9 parameters of the immunological status by key laboratory parameters.In this case, lymphocytes were associated with leukocytes, T-cells, which seems quite understandable, taking into consideration the origin of these cells. T-helper cellswere positively associated with leukocytes, T-cells, NBTact; NBTsp correlated with NBTact, with segmented nuclei, leukocytes, IgG, and PI (Zemskov *et al*., 2013).

With the combination of nephrolithiasis with chronic pyelonephritis

The conjugate dynamics of Tcytotoxic - with leukocytes, lymphocytes, IgG; IgM - with T-h, IgG, MSM; IgG- with IgA, IgM, CIC, and PN, respectively, was established. Surgical treatment - distal lithotripsy not only changed the range of key indicators in patients, but also modified the range of their interrelations. The dynamics of general leukocytes was positively consistent with the number of lymphocytes, eosinophils, stab cells, T-cells. NK, CIC, T-h - with were associated with lymphocytes and IgM. Additional supply of patients with *lycopid* changed the quality of the coordinated variations of the components of the immuno-laboratory status from the level of action of remote lithotripsy.

So, T-lymphocytes were associated with the dynamics of eosinophils, IgM, T-h. The dynamics of NK cells was consistent with leukocytes, T-cells. The concentration of MWM in the blood serum was related to the content of IgM, IgG, CIC, and PN. Under similar conditions, *derinat* determined the correlation of leukocyte counts with the dynamics of the level of lymphocytes, T-cells, NK, phagocytes;CD11b+ lymphocytes - with leukocytes, IgG, PN, NBTsp; Ig concentration was found to be associated with IgM and B-lymphocytes. The combination of *lycopid* with *derinat* led to the formation of a limiting number of significant associations of immune-laboratory status. At the same time, the number of lymphocytes correlated with the number of T-B cells, NK, eosinophilic leukocytes;Tcytotoxic, proved to be associated with T lymphocytes, T-h, NK cells, IgG, CIC. In turn, CD11b+ lymphocytes consistently changed with the number of monocytes, the magnitude of the parameters characterizing the oxygen-producing capacity of neutrophils (Khromov, 2009).

Gastric ulcer and duodenal ulcer

In patients with this pathology in an acute period,there is a decrease in the content of plasma RNA, an increase in the level of ribonucleotides in gastric or intestinal contents, the accumulation of cAMP in the intestinal mucosa adjacent to the ulcerative defect, and an increase in 17-OCS (oxycorticosteroids)in urine. In the immune system, at the same time, the quantitative and functional deficiency of the T-link of immunity is determined, the number of zero lymphocytes increases, the IgA content decreases. A direct strong correlation

was revealed between the number of leukocytes, T-cells, IgA concentration and RNA content in blood plasma, the inverse relationship between the level of null lymphocytes and ribonucleotides. The appointment of patients with *sodium nucleinate (Na salt of yeast RNA)* corrects the initial deficiency of plasma RNA, T-cells, IgA, and reduces the excess level of null lymphocytes, which is combined with the achievement of clinical remission of the disease (Zemskov *et al.*, 2016).

Urogenital viral (herpes) infection with chlamydia (UVHI)

In the combination of these diseases, the duration of the regression of the rashes was dependent on the number of CD4+ and CD15+ lymphoid cells; the duration of remission of the disease – on T-h, CD95+ lymphocytes (expression of the marker of apoptosis). At the same time, the duration of subjective sensations in patients with this combination of diseases was dependent on phagocytic parameters –PI and PN, NBTsp. In the complication of UVHI with trichomoniasis, the duration of regression of the rashes and the clinical index were associated with the content of CD95+ lymphocytes, but the quality of life - with the same lymphocytes and HLA-DR+ lymphocytes. The quality of patients`life – also with NBTsp level (Zemskov *et al.*, 2013).

Naturally there is a question about the certain unified mechanism that regulates metabolic and other processes in the body, in its cells, including immune competent ones. This is a system of cyclic nucleotides: 3′5′-adenosine monophosphate (3′5′-AMP) and 3′5′-guanosine monophosphate (3′5′-GMP). These compounds can be considered as secondary intracellular messengers, which mediate the action of extracellular factors. The formation of cyclic nucleotides is associated with the activity of enzymes, adenylate cyclase and guanylate cyclases, which are components of cell membranes. Activators of adenylate cyclase are β2 - adrenergic stimulants, catecholamines, hormones of the anterior lobe of the pituitary gland, glucagon, vasopressin, prostaglandins E, parathyroid hormone, histamine and other biologically active substances. Guanylate cyclases activated by cholinergic stimulants: acetylcholine, prostaglandins E, steroid hormones and a number of other compounds. An enzyme hydrolyzing cyclic nucleotides to inactive 5′-AMP and 5′-GMP is phosphodiesterase. In general, cAMP inhibits the immune system reactions, and cGMP stimulate them.

Thus, the deficiency of 3′5′-AMP in the body during diseases is an unfavorable factor. To this we should add that this system, as a result of the action of certain hormones, for example, the glucagon product of the pancreas, regulates carbohydrate and lipid metabolism, which also plays a certain role in diseases (Zemskov *et al.* 2007).

CONCLUSION

The method of determining strong correlation relations, with a coefficient of> 0.6, of patients' indices is an additional tool for evaluating the integrating function of the immune system as a whole. Evaluation of the formation of intra-system (between immunological), inter-system (between immunological, biochemical, etc.), extra-systemic (between immunological and clinical indicators) relationships reflects the various facets of this process. For example, the long-established fact of extra-systemic immune-neuro-endocrine regulation of the body

function as a whole has an applied aspect - the possibility of directional influence on anaphylaxis through immunological, neurogenic, endocrinologicalmechanisms. The links between nucleic acid metabolism, cyclic nucleotides, lipid peroxidation, antioxidant system, biogenic amines, and immunological parameters revealed during bronchopulmonary pathology create prerequisites for the therapeutic use of these metabolic chains. The presence of direct correlation between the ribonucleotide deficiency in the blood with the presence of ulcerative defects, the number of zero lymphocytes and the inverse - with mature T-cells in patients with peptic ulcer reveals the pathogenetic role of low-molecular RNA in the maturation of lymphocytes, the formation of dystrophic processes, substantiates the clinical use of nucleic acids.

Evaluation of the coordinated dynamics of clinical and laboratory parameters in children makes it possible to establish the link between the formation of immunological disorders in them and the development of infectious-somatic diseases with gynecological pathology, complications of maternal pregnancy and provision of resuscitation (artificial ventilation) to the child. Investigation of intra-systemic associations of immunophenotyped lymphocytes with immune globulins, phagocytosis, local and systemic cytokines, deciphers the mechanisms of regulation of immune system functions in conditions of mono- and associated pathology, traditional non-immunotropic, complex modulating treatment, and allows to establish its key targets, develop indications for the choice of effective drugs.

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