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The State of the Immune Status in Patients Infected with Covid-19 with Acute Rhinosinusitis

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Abstract: The immune status has been studied at 25 COVID-19 of patients with ARS. The control group of comparison consisted from 14 practically healthy faces. At a HIV-infected of patients with ARS has revealed deep infringements of the immune status, especially from the T-link of immunity and its subpopulations, and also frustration humoral an immunity link, suppression of proinflammatory cytokine IL-10 and increase proinflammatory IFN-γ. Under the influence of the spent treatment have not revealed certain changes from the immune status at patients. It is possible to ascertain only positive changes of maintenance IL-10 and parallel decrease IFN-γ in dynamics of treatment.

Keywords: The immune status, COVID-19, acute rhinosinusitis, cellular immunity, humoral immunity, an immunodeficiency, cytokines.

In response to the introduction of an infectious agent, an inflammatory process develops, which is characterized by a number of protective mechanisms: a change in the permeability of the vascular wall, increased blood flow, increased activity of macrophages and polymorphonuclear cell elements, the release of inflammatory mediators, free oxygen radicals. Macrophages, through the release of cytokines, play a major role in the defense mechanism, causing an increase in the level of T–lymphocytes. The occurrence of nonspecific infectious and inflammatory diseases of the pharynx and upper respiratory tract occurs due to an imbalance of local and systemic immunity [4,9,12].

The leading role in local immunity is played by cytokines acting on biochemical messengers that regulate the stimulation and inhibition of inflammatory reactions that initiate an immune response. Cytokines are produced by lymphocytes and macrophages embedded in the epithelium of the mucous membrane, the source of cytokines in saliva is serum transudate and salivary glands. Cytokines are also produced by the epithelial cells of the mucous membrane themselves upon contact with a microbe. It is important to note that the content of cytokines in saliva does not correlate with their level in the blood, which indicates the autonomy of local immunity. Viral infection can serve as an initiating factor for the attachment of a bacterial pathogen in the future[5,8].

From the point of view of modern clinical immunology, the state of immunity of the oral cavity is a mirror reflecting the state of systemic, that is, general immunity, which, in particular, is an indicator primarily of the state of immunity of the gastrointestinal and respiratory tracts.

The leading place in the structure of infectious diseases belongs to viral infections. Many respiratory viral infections have manifestations on the mucous membrane of the oral cavity, recognizing which, a dentist can be the first to diagnose the disease. As for COVID-19, we still don't know much. Unfortunately, there are more questions than answers. In this regard, we

believe that a timely study of local immunity against the background of COVID-19 during the pandemic will be able to answer many questions not only from dentists and immunologists, but also from doctors of related specialties (6,7,10).

All these factors explain the wide interest in the problem of correction of violations of local and systemic immunity. Immunomodulatory drugs include drugs that have immunotropic activity and, in therapeutic doses, restore the functions of the immune system. It is clear that immunocorrector drugs are needed that have the properties of a local vaccine — they stimulate the defenses of the oral

Acting through a system of immunological mechanisms, they cause such effects as an increase in phagocyte activity with a qualitative improvement in phagocytosis; an increase in the content of lysozyme in saliva, which has bactericidal activity, induction of interferon; stimulation and an increase in the number of immunocompetent cells responsible for the production of antibodies; stimulation and an increase in the content of sIgA, which plays a significant role in the mucosal protection system[3,4,9,11].

The aim of the study was to study the parameters of the immune system in COVID-19-infected patients with acute rhinosinusitis.

MATERIAL AND METHODS OF RESEARCH

We studied 25 patients aged 30 to 44 years of COVID-19-infected with ARS who were on inpatient treatment. Males made up 56.6%, females 43.4%. Unilateral sinus damage was observed in 57.8%, bilateral - in 42.2%. In addition to signs of inflammation, general anxiety, poor sleep, refusal of nutrition, headaches were noted. In addition to the traditional examination (general analysis of blood, urine, bacteriological and biochemical studies) all patients underwent ENT examination, according to indications - sinus probing (26.5%), radiography of the paranasal sinuses (9.6%).

In the main group there were 25 COVID-19 patients infected with ORS, and in the control group there were 14 practically healthy patients of the same age who had no history of ORS and COVID-19. All 25 COVID-19-infected patients were registered at the Bukhara Regional Infection Center. The patients received antibacterial, anti-inflammatory and local therapy in a hospital setting.

Immunological studies were carried out jointly with the Research Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan. (Tashkent).

Lymphocyte phenotyping was carried out by an indirect immunofluorescence method using monoclonal antibodies to CD receptors produced by Sorbent Ltd of the Institute of Immunology of the Ministry of Health and the SR of the Russian Federation and Medbioservice. T-lymphocytes (general population - CD3); T-helpers (subpopulation Tx – CD4); T-suppressors (subpopulation Tc – CD8); B-lymphocytes (subpopulation CD19) were determined. The immunoregulatory index (IRI), the CD4/CD8 ratio, was calculated.

The concentration of serum immunoglobulins (Ig) A, M and G was determined by radial immunodiffusion.

The level of cytokines (IFN-γ, IL-10) in peripheral blood serum was studied by enzyme immunoassay using test systems of the "Vector-Best" laboratory (Russia).

The parameters of the immune status were studied twice: before treatment and 1 month after treatment.

The obtained data were statistically processed using the Microsoft Excel 2003 computer program on an LG-Pentium IV computer. The reliability of the differences when comparing the average values was determined by the Student's t criterion. The data is presented as M ± m. The differences were considered significant at $p<0.05$.

RESEARCH RESULTS AND THEIR DISCUSSION

A retrospective analysis of the study of the immune status in COVID-19-infected patients with ARS showed that in the time before the treatment, they had significant violations of their immune system (Table 1).

COVID-19-infected with ORS patients had a 0.7-fold decrease in the absolute number of leukocytes and the relative content of lymphocytes, a twofold decrease in the absolute value of lymphocytes. This decrease was reflected in a statistically significant decrease from 2 to 3 times in the absolute values of the total pool of T(CD3)- and B(CD19)-lifocytes (Table 1).

In COVID-19-infected with ARS patients, a deep suppression of T-cell immunity in their relative expression was revealed, namely a 0.6-fold decrease in T-cells with a phenotype (CD3), an even more noticeable suppression of helper T-cells (CD4) - up to 13.8 ± 2.3% (in the control group, 34.2 ± 1.6; P<0.0001), while the content of a subpopulation of T cells - T(CD8)-cytotoxic lymphocytes exceeded the background values of the control group to a moderate extent (P>0.05).

In this regard, an inversion of the immunoregulatory index (IRI) – the CD4/CD8 ratio - occurs in this group, which leads to serious changes in the immune system of patients with COVID-19 infection combined with ORS. So, we found an imbalance of subpopulations of T cells with a decrease in their helper fraction of Tc (CD4) and an increase in the suppressor part - Tc (CD8) (Table 1). The decrease in IRI recorded by us in COVID-19-infected with ORS patients indicates functional insufficiency of cells with the phenotype of Tx(CD8), and this is a sign of a deep immunodeficiency developed in patients. In COVID-19-infected patients with acute respiratory infections, a slight activation of the subpopulation of T-killers - T k (CD16) was detected, which is probably also pathogenic in this pathology.

With regard to the B-cell component of the immune system, we can say that there was a moderate decrease, which was not statistically confirmed (P>0.05). The decrease in B (CD19) lymphocytes affected the spectrum of serum immunoglobulin (SI) levels of two classes – IgA and IgG, and the amount of IgM, on the contrary, increased (Table 1).

The data obtained by us indicate profound disorders in the functioning of the immune system in sick children with COVID-19 infection and ARS, which were reflected in the spectrum of cellular and humoral immunity factors. These disorders, apparently, can be considered as a possible fact that plays an important role in the pathogenesis of this mixed pathology in children. A decrease in the relative amount of Tc (CD4) is an aggravating factor and an unfavorable prognostic criterion. The treatment did not lead to noticeable changes in the parameters of the immune system in COVID-19-infected patients with ARS. We observed a trend in a moderate increase in individual links of cellular immunity and humoral immunity, however, the restoration of the main parameters of the immune status (Table 1). In addition, patients with CP maintained the tension of the humoral component of the immune system at p > 0.05. COVID-19-infected patients with acute respiratory viral infections showed a slight increase in T(CD3) and B(CD19) in their relative and absolute values, as well as a moderate increase in the production of Tc(CD16), Tc(CD8), and Ig A concentrations (Table 1).

Table 1. Parameters of the immune system in COVID-19-infected patients with ARS in the dynamics of treatment.

Indicator	Healthy (n=14)	Patients (n=25)
Leukocytes, cl/mcl	6123 ± 162	4251 ± 321***
		4437± 234***
Lymphocytes, %	29,6 ± 1,7	21,4 ± 2,15**
		22,7 ± 2,4*
Lymphocytes, abs.	1812,4 ± 35,7	931,5 ± 97,2***
		1003,6 ± 47,5***

T(CD3), %	58,3 ± 2,5	38,4 ± 3,2***
		41,2 ± 2,7***
T(CD3), abs..	1058,2 ± 72,2	362,5 ± 43,6***
		425 ± 51,4***
Tx(CD4), %	34,2 ± 1,6	13,8 ± 2,3***
		12,4 ± 2,7***
Tc(CD8), %	22,7 ± 1,2	24,2 ± 2,8
		26,5 ± 3,1
IRI (CD4/CD 8)	1,5 ± 0,14	0,58 ± 0,31**
		0,49 ± 0,36**
Тк(CD16), %	15,4 ± 0,9	16,2 ± 2,5
		18,4 ± 3,2
B(CD19), %	24,3 ± 1,22	19,62 ± 4,4
		22,5 ± 2,6
CD19, abs..	351,6 ± 29,4	182,1 ± 20,5***
		228,7 ± 34,9**
Ig A, mg%	129,2 ± 10,8	84,4 ± 7,8**
		101,9 ± 13,6
Ig M, mg %	86,7 ± 8,9	140,4 ± 13,1***
		136,3 ± 16,5**
Ig G, mg %	1047,3 ± 33,4	888,7 ± 42,7**
		761,4 ± 54,6***
Note: in the numerator data before treatment, in the denominator - after treatment; *- P< 0.05; **- P< 0.01; *- P<0.0001 - compared with the control group;**		

Table 2. The content of pro- and anti-inflammatory cytokines in COVID-19-infected patients in combination with ORS in the dynamics of treatment.

Indicator	Control group	Main group
IFN-γ, pg/ml	23,70 ± 5,38	82,80 ± 25,07
		21,93 ± 5,28
IL-10, pg/ml	10,95 ± 3,65	86,08 ± 25,72
		52,04 ± 15,06
Table 2. The content of pro- and anti-inflammatory cytokines in COVID-19-infected patients in combination with ORS in the dynamics of treatment.		

The study of the cytokine spectrum in COVID-19-infected patients with ARS showed that they had significant differences between the values of the main group and the control group. So, for example, if in healthy children the level of IFN-γ was 23.70 ± 5.38 pg/ml, then in COVID-19-infected patients with ARS the same parameter was 3.5 times higher and was at the level of 82.80 ± 25.07 g/ml (Table 2). So, the high level of IFN-γ in HIV-infected children with ORS, it indicated the severity of the degree of inflammatory reaction.

It is known that the source of IFN-γ is activated T-lymphocytes and natural killers.Among T-lymphocytes, IFN-γ producers are both cytotoxic Tc(CD8) and Tx(CD4) cells, however, when the latter differentiate into Th1 and Th2, only Th1 cells retain the ability to produce IFN-γ.The most important function of IFN-γ is its participation in mediating the interactions between lymphocytes and macrophages, as well as in regulating the ratio of cellular and humoral components of the immune response.Being the main product of Th1 cells, IFN-γ reduces the secretory activity of Th2 cells.Thus, IFN-γ enhances the development of cellular immunity and suppresses the manifestations of humoral immunity.Therefore, IFN-γ plays an important role in immunoregulation, being a key cytokine of the cellular immune response and an inhibitor of the humoral immune response. The level of IL-10 in the COVID-19-infected patients with ARS

group was approximately 8 times higher than those of the control group. It is known that IL-10 is described as a factor stimulating B lymphocytes, since it causes the proliferation of B cells. The main producers of IL-10 are Th2 cells.

IL-10 suppresses the functions of macrophages and their secretion of IL-1, TNF and IL-6, while having an anti-inflammatory effect. IL-10 causes the proliferation and differentiation of B and T lymphocytes, affects the development of hematopoietic cells, macrophages, natural killers, basophils, being a functional antagonist of cytokines produced by Th1 cells. IL-10 promotes the development of allergic reactions, has a pronounced anti-inflammatory effect. Comparative analysis showed that the ratio of IFN-γ/ IL-10 (proinflammatory/anti-inflammatory cytokines or Th1/Th2) in healthy children was 2.2. In the presence of a pronounced inflammatory process, that is, in patients of the main group, this indicator was 0.96.A pronounced imbalance in the functioning of the main regulatory cytokines was revealed, which was expressed by a sharp rise in the level of anti-inflammatory cytokines and suppression of pro-inflammatory cytokines, which are the main regulators of acute inflammatory conditions.

So, in COVID-19-infected patients with ARS, there is a pronounced stimulation of the production of both pro-inflammatory and anti-inflammatory cytokines. Such processes can be a necessary condition for protection against an infectious agent and the systemic damaging effect of high concentrations of pro-inflammatory cytokines. After treatment in the group of COVID-19-infected patients with ORS, the level of IFN-γ approached the control values, and the level of IL-10 in the dynamics of treatment, if it decreased, but still remained at a high level, 5.5 times higher than those parameters in children of the control group.

The ratio of IFN-γ/IL-10 in the main group tended to decrease even more, amounting to 0.42.

Thus, COVID-19-infected patients with acute respiratory viral infections have a deep deficit of most parameters of the immune status. One of the main disorders on the part of the immune status is a significant suppression of Tx(CD) lymphocytes and the inversion of IRI with an increase in the functional activity of Tc(CD8) lymphocytes, which is an unfavorable clinical criterion. In these patients, there was no positive dynamics of changes in the immune status after treatment.

Under the influence of treatment, the suppression of the proinflammatory cytokine IFN-γ occurred.However, it should be emphasized that the detected change in the level of IL-10 and a violation of the quantitative ratio of pro- and anti-inflammatory cytokines indicates the presence of a pre-existing immunodeficiency condition, which, apparently, manifested itself in the form of complications against the background of COVID-19.

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