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PARAMETERS OF THE IMMUNE SYSTEM IN HIV-INFECTED CHILDREN WITH ACUTE RHINOSINUSITIS

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The aim of the research was to study immune status of 25 HIV-infected children with acute rhinosinusitis. The control group for comparison consisted of 14 practically healthy children. In HIV-infected patients with acute rhinosinusitis there have been revealed marked impairments of the immune status, especially on the part of the T-link of immunity and its subsets, as well as the disturbance of the humoral link of immunity. Under the influence of the administered treatment we have not revealed any definite changes in the immune status of the patients.

Key words: *immune status, HIV-infection, acute rhinosinusitis, cellular immunity, humoral immunity, immunodeficiency.*

Since 1983 when human immune deficiency virus (HIV) was first described in children, the epidemiology of pediatric AIDS has evolved significantly [6]. Within the last two decades of the 20-21st centuries HIV-infection of a man, a pandemic which continues to accrue, has become the leading cause of secondary immunodeficiency (SID) in children.

With the ongoing epidemic of HIV infections in the pediatric age group, providing safe and effective antiretroviral therapy for children and adolescents is crucial to save the lives of millions of children worldwide. Antiretroviral drugs have been demonstrated to significantly decrease HIV-associated morbidity and mortality, to assure normal growth and development, and to improve survival and quality of life in children and adolescents. The immunologic response to HIV infection is closely related to the child's development and creates age specific parameters for the evaluation of therapeutic response to antiretroviral therapy in pediatric HIV disease. In addition to the changes in immunological response to HIV infection, the development and maturation of organ systems involved in drug absorption, distribution, metabolism, and elimination determines significant changes in the pharmacokinetics of antiretroviral drugs throughout the childhood. Multiple factors including age-specific adherence barriers, changes in social and economic environment, as well as psychological and sexual maturation affect the treatment choices and outcomes of pediatric HIV disease [3].

Cellular immune responses play a crucial role in the control of viral replication in HIV-infected individuals. However, the virus succeeds in exploiting the immune system to its advantage and therefore, the host ultimately fails to control the virus leading to the development of terminal AIDS. The virus adopts numerous evasion mechanisms to hijack the host immune system. Defeat of immune system in HIV-infection has systemic character, appearing as deep suppression of T-cellular immunity, particularly at T-helpers [10].

Disturbances in the homeostasis of different T-cell subsets during HIV infection have been linked to immune activation. As such, several separate populations of immune cells have been correlated with immune activation, including regulatory T cells (Tregs), dendritic cells, and gut-infiltrating lymphocytes. Tregs play an important role in the development of peripheral tolerance and counter immune activation with suppressive activity. Some studies demonstrated that removal of Tregs increased HIV-specific T-cell responses [5], while others show HIV-positive individuals with low Tregs have higher immune activation [2]. Plasmacytoid dendritic cells producing type I interferon have been related to increased activation of CD8+ T cells and the progressive depletion of CD4+ T cells. A recently identified subset of T cells called Th17 cells may also be compromised by immune activation during HIV infection [12]. While systemic disturbances in the immune system are evident, the most drastic depletion of T cells occurs in the gut mucosa. Brenchley et al. [8] has recently reported that compromises to the mucosal barrier allow microbial translocation of bacterial products into systemic circulation causing immune activation. They demonstrated that plasma lipopolysaccharide and soluble CD14 correlated with systemic immune activation, and sooty mangabeys with nonpathogenic SIV (Simian Immunodeficiency Virus) infection did not have evidence of microbial translocation. Thus, several mechanisms of immune activation have been proposed, yet many questions remain unanswered.

One of the common primary symptoms of AIDS is the presence of the diseases of ENT-organs. Acute rhinosinusitis (ARS) is often revealed in children with a HIV-infection, morbidity rate in children ranges between 60-75% and lethality makes 0,01-0,2% of the patients. HIV-infected children catch ARS more often than children with normal immune system [1, 4, 9].

According to the above-mentioned facts, the study of the immune system in children with ARS and HIV proves to be topical. Classical manifestation of HIV-infection which an otolaryngologist could run into is the increase in ARS on associated with AIDS. This fact contributes the necessity of the present research [4, 11].

Aim *of the study* – to study parameters of the immune system in HIV-infected children with ARS.

Materials and methods

We investigated 25 HIV-infected children with accompanying ARS (as the first diagnostic sign of HIV infection) aging 3 to 14 years, who were hospitalized in ENT-department of the Bukhara Regional Children's Multipurpose Medical Centre. All the children had congenital HIV infection without transition to the stage of AIDS. Their mothers did not receive preventive treatment of vertical transmission of HIV infection. Boys made 56,6%, girls – 43,4%. Unilateral sinus involvement was observed in 57,8%, bilateral – at 42,2%. All patients have undergone ENT-survey, under indications - sine sounding (26,5%), X-ray of additional bosoms of a nose (9,6%).

The basic group included 25 HIV-infected patients with ARS, and controls – 14 almost healthy children of similar age who did not have ARS and a HIV in anamnesis. The patients received antiretroviral (2 or 3 times a year, the duration from 1 to 2 month), antibacterial, anti-inflammatory

and local therapies in hospital setting. HIV diagnosis was based on revealing specific antibodies as part of standard serological tests (enzyme-linked immunosorbent assay (ELISA), immune bloating in Western-bloat modification).

We carried out the immunologic studies cooperate with the Institute of Immunology at Science Academy of Uzbek Republic (Tashkent, Uzbekistan). *Phenotyping* lymphocytes was carried out by indirect immune fluorescent method by means of monoclonal antibodies to CD-receptors made by «Sorbent Ltd» (Moscow, Russia). T-lymphocytes (total set - CD3); T-helpers (subset of Th - CD4); T-suppressors (subset of Ts - CD8); T-killers (subpopulation Tk-CD16), B-lymphocytes (subset CD19) were defined. The immune regulatory index (IRI) – the ratio of CD4/CD8 was calculated.

Concentration of serum antibodies (Ig) A, M and G was defined by the method of radial immune diffusion [7]. Parameters of the immune status were studied twice: before and one month after the treatment.

The research included HIV and ARS-patients whose parents had signed the informed consent for the participation in the present research (the work was performed according to the Helsinki Declaration and approved by Ethical Committee of Bukhara State Medical Institute).

The obtained data underwent statistical processing with the use of computer program Microsoft Excel. Reliability of differences as compared to the mean values was determined by Studentrs *t* test. Data are presented in the form of M ± m. Differences were considered reliable at $p<0,05$.

Results and Discussion

The analysis of the obtained outcomes indicates that essential disturbances of the immune system functioning were revealed in HIV-infected children with ARS (table). Thus, for instance, we observed a 0,7-fold fall in the absolute number of leukocytes and the relative number of lymphocytes, double decrease in the absolute size of lymphocytes. Such decrease was reflected in statistically reliable decrease (from 2 to 3 times) of absolute values of the total pool T (CD3) - and B (CD19) - lymphocytes.

Tabl. - Parameters of the immune system in HIV-infected children with ARS in the dynamics of treatment

Indicator	Control (n=14)	Patient (n=25)
Leukocytes (10^9/l)	6,12 ± 0,162	4,25 ± 0,321***
		4,44± 0,234***
Lymphocytes (%)	29,6 ± 1,7	21,4 ± 2,15**
		22,7 ± 2,4*
Lymphocytes (10^9/l)	1,81 ± 0,036	0,93 ± 0,097***
		1,00 ± 0,048***
T(CD3) (%)	58,3 ± 2,5	38,4 ± 3,2***
		41,2 ± 2,7***
T(CD3) (10^9/l)	1,06 ± 0,072	0,36 ± 0,044***
		0,43 ± 0,051***
Th(CD4), (%)	34,4 ± 1,6	13,8 ± 2,3***
		12,4 ± 2,7***
Ts(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**
Tk(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, (10^9/l)	0,35 ± 0,029	0,18 ± 0,021***
		0,23 ± 0,035**
		0,76 ± 0,055***

The note*: in numerator the data before treatment, in denominator - after treatment;*

** p <0,05; ** p <0,01; *** p <0,001 - in comparison with control group.*

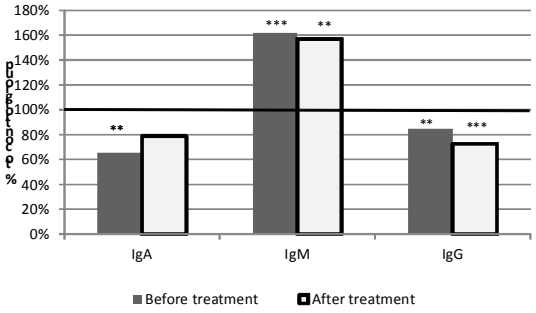
In HIV-infected children with ARS we have revealed profound suppression of T-cell immunity in their relative expression, namely, 0,6-fold reduction of T (CD3), slight suppression of Th (CD4) - up to 13,8 ± 2,3% (in the control group 34,2 ± 1,6%; $p<0,001$). The content of subset of Ts (CD8)-cytotoxic lymphocytes exceeded the baseline level in the control group at the moderate level.

Moreover, we have revealed an inversion of an immune regulatory index (IRI) – the ratio of CD4/CD8 that probably leads to serious changes in immune system of patients with HIV-infection combined with ARS. IRI reduction registered in HIV-infected children with ARS testifies to functional insufficiency of cells with a phenotype Th (CD8), and it is a sign of the profound immunodeficiency which has developed in patients. In HIV-infected patients with ARS we have revealed slight activation of subset of T-killers – Tk (CD16), which is probably *pathognomonic* in this pathology as well.

Concerning B-cell component of the immune system it can be said that moderate decrease was reflected in the spectrum of serum immunoglobulin of two classes - IgA and IgG, and on the contrary, quantity of IgM, increased (figure).

The data obtained by us testifies to profound disturbances in the functioning of the immune system of the children with a HIV-infection and ARS, which were reflected on a spectrum of cellular and humoral immunity factors. These disorders may be considered a probability factor that plays an important role in the pathogenesis of this mixed-pathology in children. The decrease in the relative quantity of Th (CD4) – is an aggravating factor, and an unfavorable prognostic criterion.

The administered treatment did not lead to considerable changes in the parameters of immune system in HIV-infected children with ARS. We observed a tendency to moderate increase in separate links of cellular immunity and humoral immunity, however, the whole recovery of basic parameters of the immune status has not occurred.



** $p<0,01$; *** $p<0,001$ - in comparison with control group

Figure - Concentration of serum antibodies in HIV-infected children with ARS in the dynamics of treatment, mg%

Conclusion

Thus, HIV-infected children with ARS show marked deficiency of most parameters of the immune status. One of the major disorders of the immune status is a significant suppression of Th (CD4)-lymphocytes and inversion of the IRI with an increase in functional activity of Ts (CD8)-lymphocytes, which is an unfavorable clinical criterion. The given patients did not have any positive dynamics of changes in the immune status after the treatment.

Our improved understanding of T-cell costimulation and coinhibition pathways attained over the past decade has given plenty of evidence on the key roles played by these molecules in immune homeostasis. However, numerous

infectious agents and tumors escape from host immune surveillance by efficiently upregulating coinhibitory signals. It is now clear that coexpression of multiple distinct inhibitory receptors is associated with greater T cell exhaustion and rapid HIV disease progression. It has also been established by researchers that T-cell inhibition results from progressive sequential accumulation of a broad array of inhibitory molecules in HIV infection.

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ПОКАЗАТЕЛИ СИСТЕМЫ ИММУНИТЕТА У ВИЧ-ИНФИЦИРОВАННЫХ ДЕТЕЙ С ОСТРЫМ РИНОСИНУСИТОМ

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Цель исследования – изучить иммунный статус у 25 ВИЧ-инфицированных детей с острым риносинуситом. Контрольную группу сравнения составили 14 практически здоровых детей. У ВИЧ-инфицированных пациентов с острым риносинуситом выявили глубокие нарушения иммунного статуса, особенно со стороны Т-звена иммунитета и его субпопуляций, а также расстройство гуморального звена иммунитета. Под влиянием проведенного лечения мы не выявили определенных изменений в иммунном статусе пациентов.

Ключевые слова: *иммунный статус, ВИЧ-инфекция, острый риносинусит, клеточный иммунитет, гуморальный иммунитет, иммунодефицит.*

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