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Dynamics of Cytokine Profile in Young Children with Acute Severe Pneumonia on the Background of Acute Herpetic Stomatitis before and after Treatment

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Abstract The purpose of this study was to study the content of pro- tumor necrosis factor alpha (TNFa) and anti-inflammatory interleukin-10 (IL-10) cytokines in peripheral blood serum in dynamics before and after conventional and combined therapy in young children with acute pneumonia on the background of acute herpetic stomatitis (OGS). Youngsters were included in the present study. The 1st group consisted of 28 young children with acute bacterial pneumonia without OGS, the 2nd included 54 children with acute pneumonia with OGS. The control group (consisted of 22 practically healthy children of analogical age). The analysis, clinical observations, X-ray, immunological. An imbalance in the production of pro- and anti-inflammatory cytokines has been established in all groups with OGS, leading to a weakening of anti-infective protection and the progression of infection. A comparative assessment of the effectiveness of traditional therapy and the significance of the use of the drug Cycloferon was carried out.

Keywords Young children, Pneumonia, Stomatitis, Herpes simplex virus, Cytokines, Immunity

1. Introduction

Respiratory diseases occupy a leading place in the structure of the overall morbidity of children. Despite great achievements in the fight against this pathology, the incidence of pneumonia in children of the first three years of life remains widespread, the pneumonic process often proceeds heavily, sometimes ends fatally.

An unfavorable background for the course of the pneumonic process in young children is rickets, protein-energy deficiency, anemia, dysbiosis, etc. They largely determine the recurrence of pneumonia in a child, the duration of their course, the tendency to exacerbations, relapses and complications.

Infection caused by the herpes simplex virus (HSV) is the most common among people (80-95% of the population are lifelong carriers of the virus). Seroepidemiological studies have shown that by the age of 15, about 83% of children are infected with HSV, and at the age of 30 and older, more than 90% of the population have antibodies to HSV of one type or another [2,4].

Most people come into contact with the virus in early childhood. The manifestation of primary herpetic infection is more often acute herpetic stomatitis (OGS), the most common in children aged 6 months to 3 years [4]. This is due to the disappearance of antibodies obtained interplacentally from the mother, with the structural features of the oral mucosa, high permeability of histohematological barriers, insufficient activity of local immunity, as well as with frequent natural violations of the integrity of the mucous membrane as a result of teething and microtrauma [3,5].

The state of the immune system plays an important role in the occurrence and nature of the course of herpetic infection. The production and secretion of proinflammatory cytokines (interferons, interleukins) belong to the earliest events in HSV infection [8,9] and influence the subsequent specific immune response.

The mutually inhibitory effect of cytokines produced by T-helpers of one type on the formation of cytokines by T-helpers of another type is widely known (for example, Th1-cytokines inhibit the formation of Th2-cytokines; and Th1- and Th2-cytokines inhibit the synthesis of Th17-cytokines) [7].

Despite the huge amount of research in this direction, today the question of the implementation of the immune response in young children with acute pneumonia against the background of OGS g remains open. In connection with the above, the purpose of this study was to study the content of pro- (TNFa) and anti-inflammatory (IL-10) cytokines in peripheral blood serum in dynamics before and after conventional and combination therapy, in children aged 6

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months to 3 years with stomatitis.

2. Material and Methods

92 young children were included in the present study. The 1st group consisted of 28 young children with acute bacterial pneumonia without HSV, the 2nd group included 54 children with acute pneumonia with OGS. The control group (consisted of 22 practically healthy children of the same age).

Immunological studies in the examined children were conducted in the laboratory of immunoregulation of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.

The concentration of tumor necrosis factor alpha (TNF) and interleukin-10 (IL-10) in the oral fluid was determined by solid-phase enzyme immunoassay using the test systems of VECTOR-BEST JSC (Russia, Novosibirsk). The quantitative evaluation of the results was carried out by constructing a calibration curve or using a commercial computer program "Microplate manager", reflecting the dependence of the optical density on the concentration for a standard antigen and allowing comparison of the studied samples with it.

Statistical processing of the obtained data was carried out using the computer program Statistica 6.0. The reliability of the differences in the average values (p) of the compared indicators was evaluated by the Student's criterion (t).

3. Results and Discussions

The body's immune response to the virus consists of two phases, where Th1/Th2 activated cells are involved, respectively. In the first phase, interferon production is stimulated and natural killer cells and other immunocompetent cells are activated [5]. Macrophages play a central role in immune defense and are involved in both nonspecific and specific immune responses against HSV infection. They respond to viral infections with rapid secretion of proinflammatory cytokines [7], which include tumor necrosis factor alpha (TNFa), which is important for primary protection.

Tumor necrosis factor α (F) is a representative of another family of immunologically significant proteins. The main producers of TNF are monocytes and macrophages. It is also secreted by neutrophils, endothelial and epithelial cells, eosinophils, mast cells, B- and T-lymphocytes when they are involved in the inflammatory process. TNFa is detected in the bloodstream before other pro—inflammatory cytokines - already 20-30 minutes after the induction of inflammation. TNFa is involved in the formation of all major local, as well as some systemic manifestations of inflammation. It activates endothelial cells, stimulates angiogenesis, enhances migration and activates leukocytes [1,7].

Significantly elevated serum TNF values were established in all groups of children. Thus, in the group of children without HSV, the range of fluctuations was revealed from 14 to 31 pg/ml with an average value of 23.3±1.05pg/ml ($p<0.001$), which is almost 2 times, and in the group of children with HSV, the range of fluctuations was from 17 to 39 pg/ml, with an average of 26.8± 0.94 pg/ml ($p<0.001$), which is almost 2.3 times higher than the control values of 11.7±0.57pg/ml (Fig. 1).

Probably, the increased concentrations of the proinflammatory cytokine TNF causes the severity of the condition of sick children with stomatitis against the background of accompanying pneumonia, and a multiple increase in the content of cachexin indicates the severity of clinical manifestations and the process of chronization.

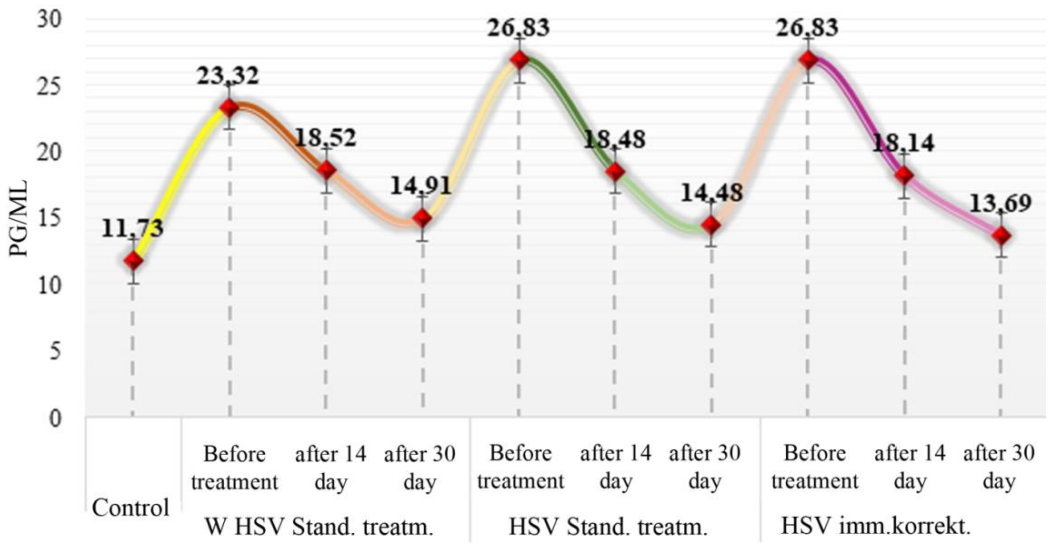

Figure 1. Dynamics of serum TNF in groups of children before and after treatment

According to international protocols, the treatment of herpetic stomatitis involves the appointment of etiotropic, pathogenetic and symptomatic agents.

In order to identify the effectiveness of treatment, a group of children without HSV were treated with conventional drugs, and the group with HSV was divided into 2 subgroups: 1st with traditional conventional treatment and 2nd with combined immunocorrecting treatment with Cycloferon 12% 6 mg/kg. To establish the effectiveness of treatment of these children, we monitored the dynamics of the studied cytokines in peripheral blood serum 14 and 30 days after the start of treatment in children of the main group and the comparison group. The results obtained are shown in Fig. 1.

Analysis of the level of TNF in the peripheral blood serum in a group of children without HSV showed that with traditional treatment after 14 days, it did not significantly decrease by 20.5% with an average of 18.52±1.28 pg/ml compared with the initial values ($p>0.05$), and 30 days after the start of treatment, synthesis decreased by 36% relative to with data before treatment with an average value of 14.91±0.69 pg/ml ($p<0.001$) (Fig. 1).

The assessment of the TNF content in the group of children with HSV found that in children with traditional treatment, after 14 days, the expression level decreased by 31.1% with an average value of 18.48±1.02 pg/ml compared with the data before treatment ($p<0.001$), and 30 days after the start of therapeutic measures, the level decreased by 46% with an average value of 14.48±0.74 pg/ml compared to the initial values ($p<0.001$) (Fig. 1).

When studying the concentration of TNF in a group of children with HSV, it was revealed that combined immunocorrecting therapy contributed to a decrease in synthesis by 32.4% after 14 days with an average of 18.14± 0.69 pg/ml compared to the initial values ($p<0.001$), and 30 days after the start of therapy, expression decreased by almost 49%, which in The average was 13.69±0.79 pg/ml compared with the data before the start of treatment ($p<0.001$) (Fig. 1).

In the second phase of the immune response, a number of immune reactions are triggered: the production of humoral specific antibodies, active T cells (enhancing or suppressing the functions of other cells), T-cell immunity reactions [5], therefore, the next stage of our research was to study the level of anti-inflammatory IL-10 in all groups of children.

Interleukin 10 – (IL-10 or IL-10) is described as an inhibitor of Th1 cell activity. The main anti-inflammatory effect of IL-10 is realized through the suppression of the activity of macrophages and T—lymphocytes (especially Th1 and Th17) - primarily the synthesis of pro-inflammatory cytokines by these cells. It is produced mainly by monocytes and, to a lesser extent, by lymphocytes, including Th2 type, mast cells, some subpopulations of activated T- and B-lymphocytes. IL-10 promotes the development of a humoral immune response; it serves as a synergist of IL-4 when acting on B cells, protecting them from apoptosis, enhancing their proliferation, differentiation into antibody-forming cells, their synthesis of IgM and IgA [7].

During the study, the serum level revealed a multidirectional synthesis of IL-10 in all groups of children with stomatitis with pneumonia. Thus, in the group of children without HSV on the background of pneumonia, the level of IL-10 exceeded the control indicators by more than 1.8 times compared with healthy children of the control group (15.46±0.77pg/ml versus 8.2±0.38pg/ml) ($P<0.001$). A lower content of anti-inflammatory IL-10 was found in children with HSV compared with healthy children of the control group (respectively 5.5±0.31pg/ml and 8.2±0.38 pg/ml) ($P<0.001$) (Fig. 2).

It should be assumed that in children with HSV, due to the low content of IL-10, they are not able to provide an anti-inflammatory effect, as a result of which inflammation tends to be more widespread and intense, there is a weak opportunity to inhibit the production of other key pro-inflammatory cytokines and neutralize the action of pathogenic agents. Probably, at the same time, the low content of IL-10 in children with HSV compared to children of the control group, cause a lower activity of the humoral link, contribute to the development of pro-inflammatory reactions and the process of chronization.

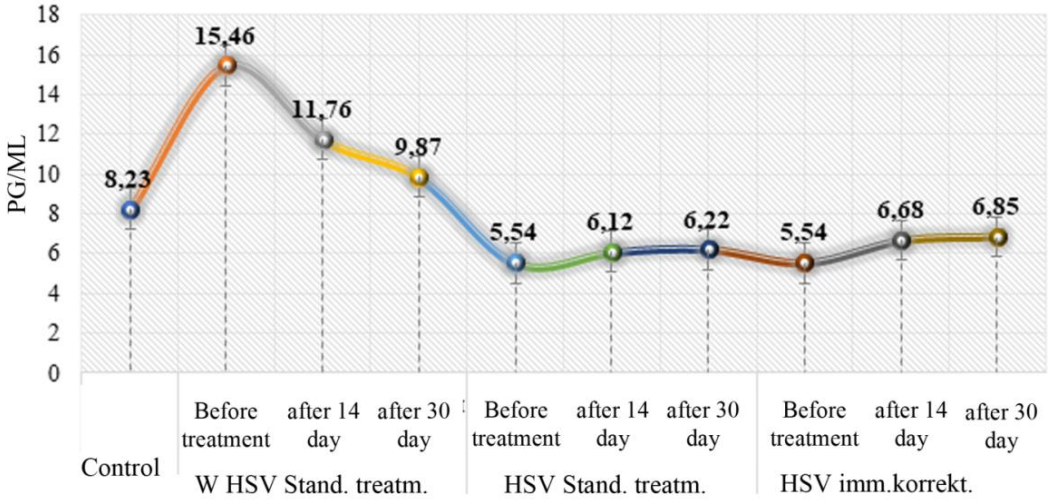

Figure 2. Dynamics of serum IL-10 in groups of children before and after treatment

The study of the serum IL-10 content after the start of treatment revealed the following changes, shown in Fig. 2.

Analysis of the levels of anti-inflammatory cytokine in the group of children without HSV showed that with traditional treatment after 14 days, expression significantly decreased by almost 24% with an average of 11.76±0.67 pg/ml compared with the initial values ($p>0.01$), and 30 days after the start of treatment, synthesis decreased by 36% in compared with the data before treatment with an average of 9.87±0.31 pg/ml ($p<0.001$) (Fig. 2).

Analysis of IL-10 content in a group of children with HSV with traditional treatment revealed no significant changes, but with positive dynamics and clinical manifestations. Thus, the concentration of this cytokine increased after 14 days with an average value of 6.12±0.0.31 pg/ml, at least compared with the data before treatment ($p> 0.05$), and 30 days after the start of therapeutic measures, the level of IL-10 increased with an average value of 6.22±0.41 pg/ml compared with the initial indicators ($p>0.05$) (Fig. 2).

Evaluation of the serum concentration of IL-10 in the group of children with HSV with combined immunocorrecting therapy found that after 14 days, the indicators of this cohort of children significantly increased with an average of 6.68± 0.34 pg/ml compared with the initial values ($p> 0.01$), and 30 days after the start of therapy, synthesis increased, with an average the indicator is 6.85± 0.48 pg / ml in comparison with the indicators before the start of treatment ($p < 0.01$) (Fig. 2).

The results obtained indicate that despite the fact that statistical reliability has not been established in the group of children with HSV with traditional treatment and the revealed reliability in the group with combined immunocorrective treatment, an increase in IL-10 after therapy suggests an increase in the activity of the humoral link, a restriction of TNF production and a reduction in the formation of pro-inflammatory reactions, the process of chronization, and also increases the ability to neutralize the effect of HSV on the child's body.

Thus, the results obtained suggest that during therapy in children with stomatitis of various etiologies for 30 days, despite the fact that the indicators of all groups remained above the standard values, they had a positive trend. The study of the state of systemic immunity in children after the initiated therapy allowed us to clarify the characteristic dynamics in this disease. The revealed patterns of cytokine dynamics, established in peripheral blood serum, allow us to consider pathogenetically justified the inclusion of cycloferon 12,% intramuscularly and intravenously in the complex treatment regimen of herpetic stomatitis, aimed at their correction.

4. Conclusions

1. An imbalance of Th1/Th2 cytokine production was established in children with stomatitis with pneumonia of various etiologies before treatment.
2. Significantly increased serum TNF content was revealed in all groups of children with stomatitis before treatment.
3. The study of IL-10 concentration established multidirectional indicators before treatment in a group of children without MIC and with HSV.
4. Analysis of the data obtained after the start of treatment determined that in groups of children without HSV with traditional treatment, the level of TNF and IL-10 decreased.
5. Assessment of TNF and IL-10 levels in the group of children with HSV with combined immunocorrecting therapy established a significant decrease in pro-inflammatory and a significant increase in anti-inflammatory cytokines.

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