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CHANGES IN THE SPECTRUM OF CYTOKINES IN PRIMARY AND RECURRENT LARYNGOTRACHEITIS IN CHILDREN

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Abstract. *The peculiarity of the immune status in recurrent stenosing laryngotracheitis (RSLT) is manifested in a long-term selective deficiency of IgA, including in combination with a high level of IgE, a decrease in phagocytosis, and an increase in concentration. ASLT in children is characterized by an increase in the level of B-lymphocytes and hyperproduction of IgA, IgG and IgE, as well as IL-4. The level of cytokines in the secretion of the oral cavity - IL1β, TNF-α and IL-4 is sharply increased in children with RSLT.*

Keywords: *acute stenosing laryngotracheitis, primary stenosing laryngotracheitis, recurrent stenosing laryngotracheitis. In this article.*

ИЗМЕНЕНИЯ СПЕКТРА ЦИТОКИНОВ ПРИ ПЕРВИЧНЫХ И РЕЦИДИВИРУЮЩИХ ЛАРИНГОТРАХЕИТАХ У ДЕТЕЙ

Аннотация. *Особенность иммунного статуса при рецидивирующих СЛТ проявляется в длительно сохраняющемся селективном дефиците IgA, в том числе в сочетании с высоким уровнем IgE, снижением показателей фагоцитоза, повышением концентрации. ОСЛТ у детей характеризуются повышением уровня В-лимфоцитов и гиперпродукцией IgA, IgG и IgE, а также IL-4. Уровень цитокинов в секрете ротовой полости – IL1β, TNF-α и ИЛ-4 резко повышен у детей с РСЛТ.*

Ключевые слова: *острый стенозирующий ларинготрахеит, первичный стенозирующий ларинготрахеит, рецидивирующий стенозирующий ларинготрахеит.*

INTRODUCTION

The study of the role of cytokines in acute stenosing laryngotracheitis (ASLT) in children is one of the fundamental points for understanding the pathogenesis of viral infections and the nature of the pathogenicity of viruses [1, 4, 5, 6]. For clinical practice, the study of the role of cytokine status is difficult to overestimate, since it reflects individually, the primary reaction to a viral agent, allows you to assess the nature of the course of the process and predict the outcome of the disease in many viral infections, as well as to objectively evaluate the effectiveness of therapy.[1, 9].

In this regard, the purpose of our study was to study the role of cytokines in the pathogenesis of acute stenosing laryngotracheitis.

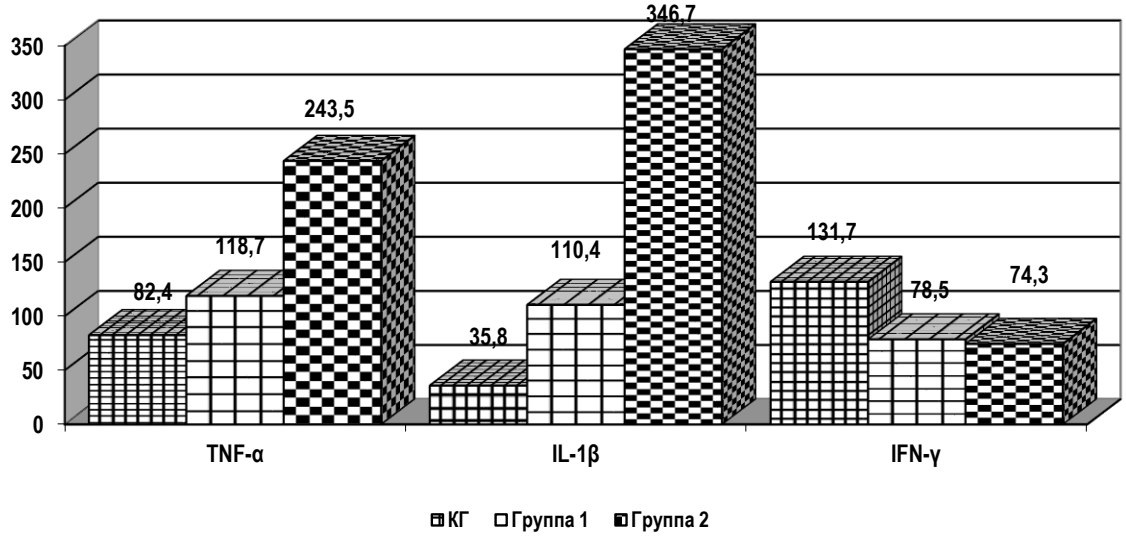
MATERIALS AND METHODS

The study is based on a clinical and laboratory examination of 275 children with acute stenosing laryngotracheitis who were admitted to the City Infectious Diseases Hospital No. 3 in the period from 2011 to 2014.

All examined children were divided into 2 groups according to the forms of acute stenosing laryngotracheitis according to the classification of Yu.V. Mitina (1986) Group 1 - 122 children with primary stenosing laryngotracheitis, Group 2 - 153 children with recurrent stenosing laryngotracheitis.

All immunological indicators, including interferon α and γ: the level of antiviral (α-IFN) and pro-inflammatory (γ-IFN) interferons in peripheral blood serum were studied by enzyme immunoassay using Vector-Best test systems (Novosibirsk, Russia). To establish the role of the cytokine link in the pathogenesis of acute and recurrent OSLT in children, we determined the level of interferons IFN-α and IFN-γ, the level of IL-4 and the level of pro-inflammatory cytokines: IL-1β, IL-6.

Our data demonstrate a significant dependence of the concentration of the level of pro-inflammatory cytokines in the blood serum on the form of OSLT. Particularly pronounced disorders were noted in children with RSLT. The revealed changes significantly differed from the values obtained in the group of children with PSLT (Fig. 1).



1. The content of TNF-α, IL-1β and IFN-γ in the blood serum of children,

ASLT patients depending on the form of the disease

Our data demonstrate a significant dependence of the concentration of the level of pro-inflammatory cytokines in the blood serum on the form of ASLT. Particularly pronounced disorders were noted in children with RSLT. The revealed changes differed significantly from the values obtained in the group of children with PSLT.

So, if during RSLT the level of serum TNF-α in the examined children was significantly higher (243.5±23.9 pg/ml compared with the data of children in the control group - 82.4±7.0 pg/ml, $P<0.001$) , then with PSLT only a moderate increase in this cytokine was noted (118.7±9.3 pg/ml, compared with the control $P<0.05$).

When analyzing the results of the study of the level of IL-1β in the blood serum, it was found that in children with RSLT there is an almost tenfold increase in its level compared to the control - 346.7±36.6 pg/ml, against 35.8±3.9 pg /ml ($P<0.001$). In children with PSLT, there was an increase in the level of IL-1β by more than 3 times compared with the control group of children - 110.4±8.3 pg/ml ($P<0.001$).

As is known, IFN-γ is produced by activated Th1 cells and NK cells. In our studies, a reduced level of IFN-γ compared with the control group of children was noted. Moreover, this decrease is observed in ASLT: with RSLT - 74.3±4.9 pg/ml (P<0.001), with PSLT - 78.5±7.3 pg/ml (P<0.001). The level of IFN-γ, while in the control group of children, on average, was 131.7±11.0 pg/ml.

RESULTS

When analyzing the level of a number of inflammatory cytokines in the blood serum of children with ASLT, compared with the control, we noted a significant significant increase in the level of TNFα and IL-1β with RSLT and a moderate increase in their serum levels with PSLT.

The serum level of IFN-γ in ASLT was significantly lower than in the control group and did not depend on its form.

Of particular interest was the study in children with ASLT of the level of IgE in the blood and the concentration of IL-4 in various biological fluids as markers of inflammation activity.

The results of the study of the levels of IL-4 in the blood serum and in the smear, as well as the level of total IgE in the blood serum of all examined children are presented in.

As can be seen from the table, elevated levels of total IgE are detected in the peripheral blood of sick children. The highest level is noted in the group of children with PSLT (362.0±19.5 IU/l), which significantly exceeds the value of this indicator in children with PSLT (308.0±13.5 IU/l) (P<0.05) and with the indicators of the control group (103.0±6.12 IU/l) (P<0.001).

Thus, with RSLT, there is a higher content of IgE in the blood serum compared with children with PSLT.

The content of IL-4 and IgE in biological fluids of children with ASLT

Показатели	Контрольная группа (n=40)	1 группа (n=122)	2 группа (n=153)
IL-4 (мазок), пг/мл	0	310,0±13,5***	76,0±3,6***^^^
IL-4 сыворотка крови, пг/мл	2,85±0,19	12,0±0,38***	15,1±0,63***^^^
IgE в сыворотке крови, МЕ/л	103,0±6,12	308,0±13,5***	362,0±19,5***^

Note: * - differencesrelative to the data of the control group are significant (* - P<0.05, ** - P<0.01, *** - P<0.001); ^ - differences between the data of groups 1 and 2 are significant (^ - P<0.05, ^^ - P<0.01, ^^^ - P<0.001)

When studying the level of IL-4 in blood serum in children, a similar pattern was revealed: the highest level of IL-4 is typical for children with RSLT (15.1±0.63 pg/ml), which significantly (P<0.001) exceeds the value of this indicator in children with PSLT (12.0±0.38 pg/ml).

In contrast to peripheral blood, in a smear taken from as close as possible to the focus of inflammation, the level of IL-4 is significantly (P<0.001) higher in children with PSLT (310.0±13.5 pg/ml) compared with the data of children suffering from RSLT (76.0±3.6 pg/ml).

Induced secretion depends on the nature of the stimulus, manifesting itself differently for different cytokines and different types of epithelial cells.

A few studies related to the pathology of the oral mucosa are devoted to the clinical study of the level of cytokines in the oral cavity [2].

We have studied the cytokine profile of oral secretions in children with ASLT in projection on the severity and stage of the disease (activation-remission). The content of three cytokines, IL-1β, TNFα, and IL-4, was analyzed.

They were chosen as probable markers of total (IL-1β, TNFα) and allergen (IgE)-dependent phlogogenicity (IL-4).

In the group of healthy children, the content of IL-1β in saliva was 21.8±1.80 pg/ml. According to the groups of patients, the following results were obtained: group 2 — 196.0±20.76 pg/ml, group 1 — 128.0±14.04 pg/ml (for all indicators P<0.001). Differences between groups are significant (P<0.01).

Cytokines in oral secretions in children with ASLT depending on the form of the disease.

Показатели цитокинов, пг/мл	Контрольная Группа	1 группа	2 группа
IL-1β	21,8±1,80	128,0±14,04***	196,0±20,76***^^
TNFα	27,3±2,55	54,6±4,56***	95,7±9,16***^^^
IL-4	6,2±0,41	12,7±1,02***	19,5±1,79***^^

Note: * - differences relative to the data of the control group are significant (* - P<0.05, ** - P<0.01, *** - P<0.001) Note: * - differences relative to the data of the control group are significant (* - P<0.05, ** - P<0.01, *** - P<0.001)

In the control group, the content of TNFα in saliva was 27.3±2.55 pg/ml. According to the groups of patients, the following results were obtained: group 2 - 95.7±9.16 pg/ml, group 1 - 54.6±4.56 pg/ml (for all indicators P<0.001).

In healthy children, the content of IL-4 in saliva was 6.2±0.41 pg/ml. According to the groups of patients, the following results were obtained: group 2 - 19.5±1.79 pg/ml, group 1 - 12.7±1.02 pg/ml (for all indicators P<0.001).

The obtained data develop the idea that the state of real homeostasis can be an indicator of distant pathological processes [2], including allergic inflammation [1].

DISCUSSION

In the present study, this manifested itself in the study of the cytokine profile (IL-1β, TNFα and IL-4) of oral secretions in children with ASLT.

It was found that, in the acute phase of the disease, the content of all three cytokines increased significantly, the most significant and constant increase was noted for IL-1β.

In patients with severe disease, cytokine levels were higher than in moderate and mild forms of the disease, no significant differences were found for the last two groups. This was observed for all types of cytokines. The difference is that mild forms of the disease usually did not cause an increase in serum levels of IL-1α and TNFα.

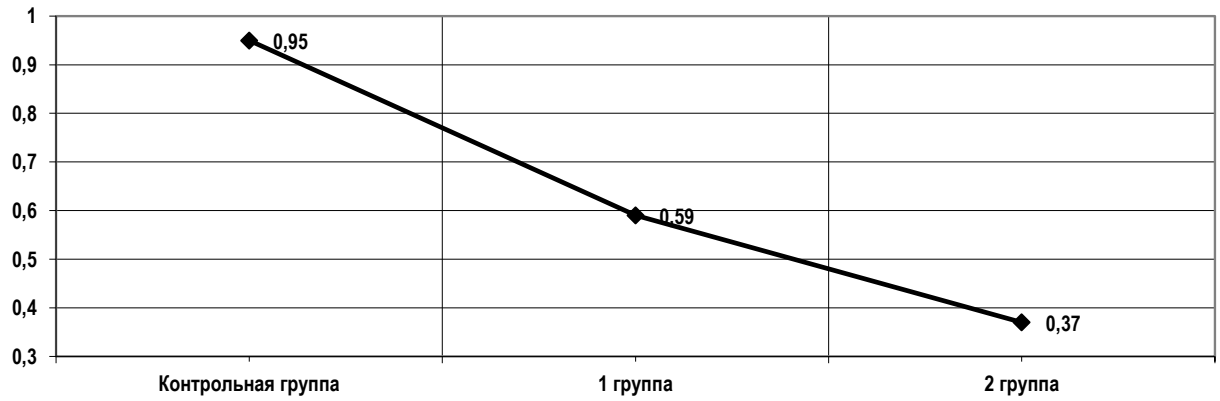
According to the literature, during an inflammatory reaction, to a greater extent due to the action of an infectious agent and to a lesser extent due to atopic inflammation, IFN-γ, activating

the macrophage link of immunity, is a direct inducer of IL-1β synthesis [3, 7]. Under physiological conditions, IL-1β is able to enhance the production of IFN-γ by activating Th1 cells.

Based on the foregoing, it seemed interesting to us to conduct a correlation study between the concentrations of these cytokines depending on the form of ASLT.

The conducted correlation analysis made it possible to establish the presence of a direct relationship between the content of IFN-γ and IL-1β in the blood serum. We found that the strength of this bond is inversely proportional to the shape of the ASLT. So, if in the control group the correlation coefficient was close to unity (r=0.95), then in groups 1 and 2, the values of the correlation coefficient were 0.59 and 0.37, respectively. Significant correlation coefficients between other pairs of cytokine levels were not obtained in any group.

Therefore, the results of the study confirm the existence of a relationship between the concentrations of IFN-γ and IL-1β, and this dependence is direct and decreases depending on the form of ASLT, which indicates violations of immunoregulatory mechanisms, and a reduced concentration of serum INF-γ indicates a violation of IL-1β mediated production of IFN-γ Th-1 cells.



Picture. 2. Values of the correlation coefficient (r) between the serum levels of IFN-γ and IL-1β in various forms of ASLT.

It is possible that the activation of the macrophage link of immunity, which occurs during ASLT, can contribute to an increase in the production by macrophages of substances that inhibit the synthesis of IFN-γ.

Thus, it was found that the majority of children with ASLT have a reduced content of T-cells. A low content of CD3+ cells indicates a reduction in the pool of circulating T-lymphocytes and, therefore, a possible risk of their insufficiency if an intensive immune response is required. A decrease in the content of functionally active T cells naturally affects the content of specialized phenotypes that perform helper and suppressor functions.

Undoubtedly, a decrease or increase in their number can have a negative impact and, in all likelihood, is one of the pathogenetic factors of the inflammatory process. As is known, NK cells play an important role in anti-infective protection, and their changes in both directions are apparently due to several reasons: partial immunodeficiency, insufficient production of non-toxic antibodies that block the activity of immunocompetent cells.

CONCLUSIONS

Our results show a significant dependence of the concentration of the level of pro-inflammatory cytokines in the blood serum on the form of OS LT.

The results of the study confirm the existence of a relationship between the concentrations of IFN-γ and IL-1β, and this dependence is direct and decreases depending on the form of ASLT, which indicates violations of immunoregulatory mechanisms.

Thus, our results indicate a violation of metabolic processes and pronounced immunological changes that contribute to the development of complications of this disease.

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