



**CLINICAL, DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF
CYTOKINE INDICATORS IN PRIMARY AND RECURRENT STENOSING
LARYNGOTRACHEITIS IN CHILDREN**

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Abstract: In recent years, against the background of the growing incidence of acute respiratory viral infections (ARVI), acute stenosing laryngotracheitis of viral etiology has attracted special attention from pediatricians and pediatric otolaryngologists. The frequency of such diseases, according to various studies, varies from 0.1% to 0.4% among all hospitalized children diagnosed with acute respiratory viral infection (ARVI). The development of stenosing laryngotracheitis in ARVI significantly worsens the condition of patients, the symptoms of this disease predominate in the clinical picture, and in some cases, the child's life depends on its outcome.

Keywords: subpopulations of T-lymphocytes - T-helpers and T-suppressors, $\text{INF-}\alpha$, degree of immune disorders, OSLT, PSLT.

Annotatsiya: So'nggi yillarda o'tkir respirator virusli infeksiyalar (ARVI) bilan kasallanishning ko'payishi fonida virusli etiologiyaning o'tkir stenzli laringotraxeitlari pediatrlar va bolalar otorinologlarining alohida e'tiborini tortdi. Bunday kasalliklarning tarqalishi, turli tadqiqotlarga ko'ra, o'tkir respirator virusli infeksiya (ARVI) tashxisi qo'yilgan kasalxonaga yotqizilgan barcha bolalar orasida 0.1% dan 0.4% gacha. ARVI paytida stenzli laringotraxeitning rivojlanishi bemorlarning ahvolini



sezilarli darajada yomonlashtiradi, bu kasallikning belgilari klinik ko'rinishda ustunlik qiladi va ba'zi hollarda bolaning hayoti uning natijasiga bog'liq.

Kalit says: T-limfotsitlarning subpopulyatsiyalari - T-xelperlar va T-suppressorlar, INF-a, immunitetning buzilishi darajasi, OSLT, PSLT.

Introduction.

The state of the immune system plays a key role in the development of acute stenosing laryngotracheitis. Studies show a significant decrease in the total number of T-lymphocytes [6, 11] and a violation of the humoral response: disimmunoglobulinemia with a decrease in IgA and IgG with an increased level of IgM is observed. A decrease in the latter indicator is especially characteristic in uncomplicated cases.

Factors contributing to the development of ASLT include peri- and postnatal conditions: pneumopathy (including artificial ventilation of the lungs), severe forms of perinatal CNS damage [8], the presence of thymomegaly. These factors negatively affect the adaptive reactions of the body.

The problem of acute stenosing laryngotracheitis in children is complicated by the lack of a unified approach to treatment and diagnosis, as well as changes in immune status: a decrease in gamma globulins, IgA and IgG with an increased level of total IgE [9].

Materials and research methods.

In a scientific study, immunological tests were performed on 275 young patients with acute laryngotracheitis. The researchers assessed both cellular and humoral components of immunity as follows:

- determination of the percentage of lymphocytes in the blood;
- quantitative measurement of T-lymphocytes (including their subtype characteristics - CD3+, CD4+ and CD8+) with the isolation of T-helpers and T-suppressors, which was carried out using monoclonal antibodies;
- analysis of immunological markers on the cell surface (for example, CD25, CD95) according to the method of F. Yu. Garib and his colleagues.



To assess the humoral response, serum immunoglobulin A, M, and G levels were measured.

Besides:

- to determine the concentrations of interferons α and γ in the blood, an enzyme-linked immunosorbent assay was used using the Vector-Best test system (Novosibirsk), taking into account their importance in the body's antiviral defense;

- to study cytokines, modern methods of solid-phase enzyme-linked immunosorbent assay were used, including fixation of monoclonal antibodies on plates and subsequent determination of concentrations of various cytokines.

These studies made it possible to comprehensively assess the state of the immune system in children with acute stenotic laryngotracheitis (ASLT).

Discussion and results.

In the context of acute stenotic laryngotracheitis in children (ASLT), the key aspect remains understanding the immunological disorders and their impact on the course of the disease. Many of the mechanisms of the immune system in ASLT have not yet been sufficiently studied, which creates significant scientific and practical interest in this problem [4]. The main goal of such studies is to identify patterns in the functioning of the immune system in this group of patients to optimize treatment approaches.

According to the immune response regulation theory, T helper lymphocytes (Th) play a crucial role, Th1 cells activate the cellular response, and B helper lymphocytes (Th2) support humoral immunity.

Cytokines such as tumor necrosis factor alpha (TNF- α), γ -interferon (IFN- γ), interleukins IL-1 β and IL-4 are regulators of the immune response type. These molecules provide interaction between the cellular and humoral components of immunity.

In our study, to assess the influence of the cytokine profile on the development of primary and recurrent forms of OSLT in children, the following were determined:

- Interferon level: α (IFN- α) – antiviral action
- The level of γ -interferon (IFN- γ) – activation of cellular immunity



- Concentration of IL-4, which supports the humoral response
- Content of proinflammatory cytokines: IL-1β and IL-6

Such a comprehensive assessment will allow for a deeper understanding of the mechanisms of OSLT development in children and the development of more effective treatment strategies (Fig. 1).

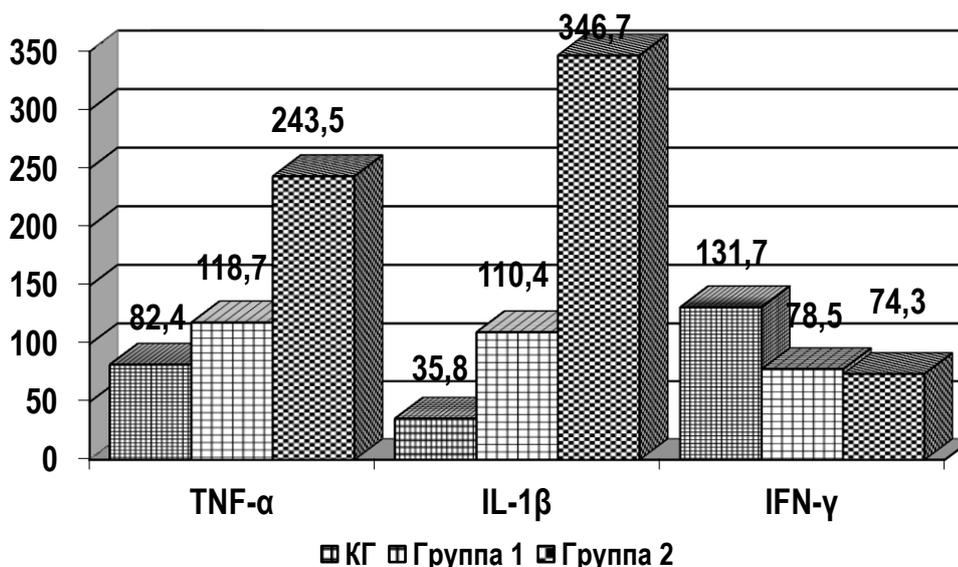


Fig. 1. Content of TNF-α, IL-1β and IFN-γ in the blood serum of children with ASLT depending on the form of the disease.

The study showed significant differences in the level of proinflammatory cytokines in children with various forms of acute respiratory allergic diseases (ARDS). In patients suffering from the respiratory form of allergy (respiratory sensitization), a sharp increase in the concentration of TNF-α and IL-1β cytokines is noted, for example, the level of TNF-α was 243.5 ± 23.9 pg / ml in children with respiratory allergy versus 82.4 ± 7.0 pg / ml in the control group ($P < 0.001$), and the concentration of IL-1β reached almost ten times greater - 346.7 ± 36.6 pg / ml versus 35.8 ± 3.9 pg / ml in the control group ($P < 0.001$).

In case of food sensitization, a less pronounced increase is observed for TNF-α — up to 118.7 ± 9.3 pg/ml ($P < 0.05$), and for IL-1β — more than three times compared to the control group: 110.4 ± 8.3 pg/ml ($P < 0.001$). The level of interferon-γ (IFN-γ) in



children with both forms of ARI is significantly reduced, for example, for the respiratory form — up to 74.3 ± 4.9 pg/ml and for the food form — up to 78.5 ± 7.3 pg/ml, while in the control group this figure is 131.7 ± 11.0 pg/ml ($P < 0.001$).

Thus, the results indicate the predominance of Th2 T-lymphocyte activation in ARI and the involvement of IL-4 in the initiation of IgE synthesis by B-lymphocytes. This contributes to increased activity of mast cells, basophils and eosinophils.

The study revealed significant differences in the concentrations of proinflammatory cytokines in children with different forms of acute respiratory allergic reactions. This was especially evident for patients suffering from the respiratory form: the level of TNF- α increased to 243.5 ± 23.9 pg/ml (in the control group - only 82.4 ± 7.0 pg/ml), which is confirmed by statistically significant $P < 0.001$. A significant increase was also observed for IL-1 β , almost ten times more compared to the control (346.7 ± 36.6 pg/ml versus 35.8 ± 3.9 pg/ml), $P < 0.001$.

In food allergies, the changes were less pronounced, for example, the concentration of TNF- α was only 118.7 ± 9.3 pg/ml ($P < 0.05$), for IL-1 β a three-fold increase was noted - up to 110.4 ± 8.3 pg/ml compared to the control group ($P < 0.001$).

The level of interferon- γ (IFN- γ) significantly decreased in both respiratory (74.3 ± 4.9 pg/ml) and food (78.5 ± 7.3 pg/ml) allergies, compared with the control group - 131.7 ± 11.0 pg/ml ($P < 0.001$ for both forms).

These data indicate the predominance of Th2 T-lymphocyte activation in acute respiratory allergic diseases. IL-4 plays an important role in stimulating IgE synthesis by B-cells, which leads to increased activity of mast cells and eosinophils.

These processes increase inflammation in the respiratory tract and contribute to the development of an allergic reaction.

Thus, IL-4 and total IgE levels may serve as important markers of inflammation, making them relevant for the diagnosis and monitoring of allergic diseases.

The study showed elevated concentrations of total IgE and interleukin-4 (IL-4) in the blood of children with long-term respiratory syndrome. The level of total IgE in this



group was 362.0 ± 19.5 IU/l, which is significantly higher than the values for both children with peripheral syndrome (PSLT) – 308.0 ± 13.5 IU/l ($P < 0.05$) and the control group – 103.0 ± 6.12 IU/l ($P < 0.001$). A similar trend is observed with the level of IL-4: the highest value was in children with RSLT – 15.1 ± 0.63 pg/ml compared to children from the PSLT group (12.0 ± 0.38 pg/ml), which also differs statistically significantly ($P < 0.001$).

These data indicate that children with chronic respiratory syndrome experience significant changes in immune status.

Table 1.

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

| Indicators | Control group (n=40) | 1 group (n=122) | 2 group (n=153) |
|-----------------------------|-------------------------|------------------------|-----------------------------------|
| IL-4 (smear), pg/ml | 0 | $310.0 \pm 13.5^{***}$ | $76.0 \pm 3.6^{***\wedge\wedge}$ |
| IL-4 serum, pg/ml | 2.85 ± 0.19 | $12.0 \pm 0.38^{***}$ | $15.1 \pm 0.63^{***\wedge\wedge}$ |
| IgE in blood serum, IU/l | 103.0 ± 6.12 | $308.0 \pm 13.5^{***}$ | $362.0 \pm 19.5^{***\wedge}$ |

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

In contrast to blood samples obtained from the peripheral bloodstream, the IL-4 level in the oropharyngeal swab collected directly adjacent to the inflamed area was significantly higher ($P < 0.001$) in children with primary sclerotic lymphadenitis (PSLL) – 310.0 ± 13.5 pg/ml, while in children with recurrent sclerotic lymphadenitis (RSL) this figure was 76.0 ± 3.6 pg/ml.

Literature data on the analysis of cytokines in oropharyngeal secretion in inflammatory processes of the mucous membrane are extremely limited [3]. In our study, a comprehensive analysis was conducted, during which the cytokine profile in the



oropharyngeal secretion of children with acute sclerotic lymphadenitis was also studied, taking into account the severity and stage of the disease (primary and recurrent forms). The focus was on three key cytokines: IL-1 β , TNF- α and IL-4, which were selected as potential markers of the general inflammatory response and allergic inflammation.

In healthy children, the average IL-1 β level in saliva was 21.8 \pm 1.80 pg/ml. In sick children, the results were distributed as follows: in the group with a more severe course of the disease (group 2), the IL-1 β level was 196.0 \pm 20.76 pg/ml, in the group with a less severe course (group 1) - 128.0 \pm 14.04 pg/ml, while the statistical significance for all indicators was P<0.001. Differences between the groups are significant (P<0.01) (Table 2).

Table 2.

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

| Indicators | Control group (n=40) | 1 group (n=122) | 2 group (n=153) |
|-----------------------------|-------------------------|---------------------|-----------------------|
| IL-4 (smear), pg/ml | 0 | 310.0 \pm 13.5*** | 76.0 \pm 3.6***^^^ |
| IL-4 serum, pg/ml | 2.85 \pm 0.19 | 12.0 \pm 0.38*** | 15.1 \pm 0.63***^^^ |
| IgE in blood serum, IU/l | 103.0 \pm 6.12 | 308.0 \pm 13.5*** | 362.0 \pm 19.5***^ |

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

In a comparative analysis in the control group, the level of TNF- α in saliva was 27.3 pg/ml with an error of \pm 2.55, the IL-4 indicator was 6.2 pg/ml with an error of \pm 0.41.

- Group 1: TNF- α concentration increased to 54.6 pg/ml (P<0.001), and IL-4 to 12.7 pg/ml (P<0.001).

- Group 2: the TNF- α level reached a significantly higher value of 95.7 pg/ml (P<0.001), while the IL-4 concentration was 19.5 pg/ml (P<0.001).



Thus, in sick children, there is a significant increase in the levels of the proinflammatory cytokine TNF- α and the Th2-mediated cytokine IL-4 in saliva compared to the control group, indicating the activation of both proinflammatory and allergic processes. These data confirm that homeostasis parameters can serve as important markers of pathological processes, including allergic inflammation. In this study, a significant increase in the levels of IL-1 β , TNF- α and IL-4 in the oropharyngeal secretion was found in children with acute long-term syndrome (ALTS). The greatest increase was observed for IL-1 β , which is statistically significant. In children with respiratory syndrome of long duration (RSLT), the levels of all three cytokines were significantly higher than in children with food sensitization (FSLT), however, in FSLT, no significant changes in the levels of IL-1 and TNF- α in the serum were recorded.

According to existing data, in infectious inflammation, and to a lesser extent in atopic inflammation, IFN- γ activates macrophages, which lead to stimulation of IL-1 β synthesis. Under normal physiological conditions, IL-1 β increases the secretion and production of IFN- γ , activating Th1 cells in parallel.

The study of the relationship between cytokine concentrations (IFNs- γ and IL-1 β) in opportunistic conditions of lymphotropic viral infections showed a statistically significant positive correlation between these two molecules in the serum. In the control group, a high correlation coefficient was observed ($r = 0.95$), while in ASLT, the first type of infections had $r = 0.59$ and the second – 0.37 . At the same time, for other pairs of cytokines, no significant relationships were found. Fig. 2.

These data indicate that the level of correlation between IFN- γ and IL-1 β levels directly depends on the severity of ASLT: the more severe the form of infection, the weaker the relationship. This may indicate a disruption in the regulation of the immune response at the Th1 cell level under the influence of IL-1 β .

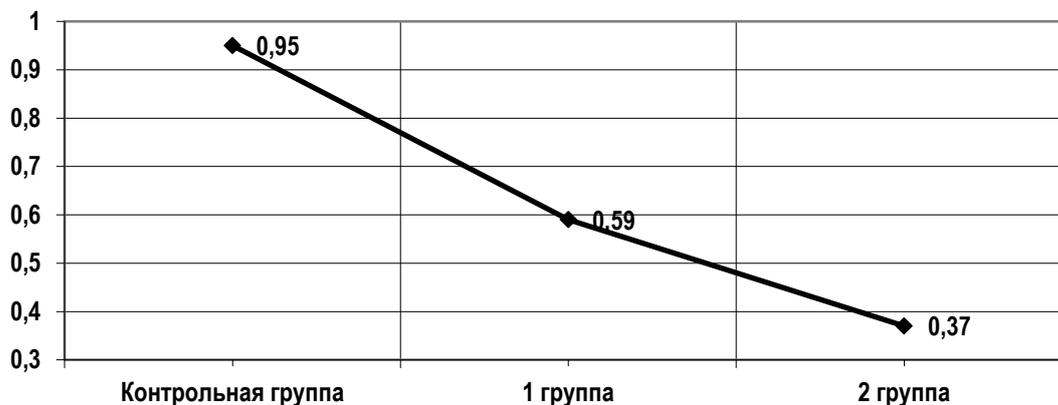


Fig. 2. Values of the correlation coefficient (r) between the content of IFN- γ and IL-1 β in the blood serum in various forms of OSLT

It is possible that activation of macrophages during OSLT leads to an increase in the synthesis of inhibitors that suppress the production of interferon- γ .

In addition, children with opportunistic conditions have a decrease in the total number of T lymphocytes and a decrease in the concentration of CD3+ cells, key indicators of immune status. This may lead to an insufficient T cell response in critical situations when increased immune involvement is required.

Changes in the number of different types of lymphocytes (T- and natural killers) reflect disturbances in the regulation of the immune process. Thus, an imbalance between Th1 and Th2 helpers can be the cause of immunopathological conditions: an excess or deficiency of cytokines of these cells leads to failures in both cellular and humoral responses.

Conclusion

Our study revealed a unique mechanism for the development of allergic reactions: activation of the Th2 subtype of T-helpers leads to the production of cytokines that predominantly suppress the cellular immune response, thereby enhancing the role of T-killers.



With a decrease in the level of T-suppressors and cytotoxic T-lymphocytes, a number of significant immunological adaptations occur. In particular, the following is observed:

- increase in the number of B-lymphocytes
- increase in the concentration of immunoglobulins IgG and IgA

These changes indicate an activated B-system of immunity, which is a key factor in the development of allergic complications. The data obtained indicate profound disturbances in immune metabolism, characterized by significant shifts in the balance of immunocompetent cells and molecules. These processes contribute not only to the occurrence of allergic diseases, but also to their progression, emphasizing the need for a comprehensive approach to therapy and prevention.

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