

## Study of the Immunological Status of Children with Acute Stenosing Laryngotracheitis and Correction of Identified Disorders

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**Abstract:** The work is devoted to the study of the state of cellular and humoral immunity in acute and recurrent laryngotracheitis in children with a further assessment of the clinical and immunological efficacy of the immunocorrective drug Ergoferon, for which a comprehensive examination and dynamic follow-up of 95 patients with laryngotracheitis were conducted. Cellular suppression and activation of humoral immunity were revealed in patients with OSLT. Patients with frequent relapses of OSLT showed significant increases in IL-4 and IL-1b levels, as well as an imbalance of interferogenesis and an increase in IgE levels. The use of an immunomodulatory drug with antiviral activity "Ergoferon" in the complex therapy of children with OSLT, especially in its recurrent course, has a beneficial effect on the clinical course of the disease, as well as on the immune status of patients.

**Keywords:** children, acute laryngotracheitis, recurrent laryngotracheitis, immune status, cytokines, immunomodulatory therapy.

**The relevance of the problem.** Acute infectious and inflammatory processes in the upper respiratory tract still form the main list of diseases in childhood, which supports the constant interest of specialists of various profiles in this pathology. Special attention of researchers and clinicians is attracted by the study of the etiopathogenetic mechanisms of acute stenosing laryngotracheitis (ASLT), which is caused primarily by the development of the life-threatening condition of acute respiratory tract stenosis in children [1,2]. According to our observations and literature data, there has recently been a clear trend towards an increase in the frequency of repeated episodes of ASLT in children, which makes it obvious that there is a need to further study the underlying mechanisms of not only the occurrence, but also the recurrence of ASLT [3,4,7].

The recurrence of laryngotracheitis contributes to the formation of chronic inflammatory processes and hyperreactivity of the upper respiratory tract, negatively affects the maturation of the child's immune system, which leads to the development of secondary immunosuppression. Each new respiratory infection provokes more and more serious disorders of the immune system, contributing to the formation of both chronic inflammatory diseases of the pharynx and respiratory allergies [5,6]. The modern concept of the etiopathogenesis of laryngotracheitis takes into account the effects of multiple infectious and allergic trigger factors, most significant in immunocompromised children. However, to date, the role of cytokine regulation in the pathogenesis of the disease has not been sufficiently studied, and the diagnostic and prognostic significance of determining cytokine spectrum parameters for the occurrence and recurrence of ASLT in children has not been clarified.

**The purpose of the work.** To study the state of cellular and humoral immunity in acute and recurrent laryngotracheitis in children with further evaluation of the clinical and immunological efficacy of the immunocorrective drug Ergoferon.

**Research materials and methods.** To achieve this goal, 95 patients with laryngotracheitis underwent a comprehensive examination and dynamic follow-up. All patients were divided into 2 groups: children with a single episode of acute laryngotracheitis (63 patients with primary acute laryngotracheitis - POL) and with recurrent acute laryngotracheitis (ROLT - 32 patients). All the children we observed were examined using general clinical research methods, followed by an assessment of anamnestic, clinical and laboratory data. In addition, an additional examination was performed, including the determination of cellular and humoral immunity (immunoglobulins IgE, IgM, IgG and IgA) in blood serum, determination of cytokine levels (IL-2, IL-4, IL-6, IFN- $\alpha$ , IFN- $\gamma$ ) before and after treatment with an immunocorrecting drug in the peripheral blood.

**The results obtained and their discussion.** An important element of regulation in the immune system is the interaction of T- and B-class lymphocytes and their subpopulations. The pathological process in TT and ROLT is accompanied by compensatory stimulation of the cellular mechanisms of the immune system. Since the absolute number of total T-lymphocytes significantly increased 1.3-fold with TT and 1.7-fold with ROLT, there was also a significant increase in the percentage of T-lymphocytes in both groups. There was a significant increase in T-helper cells ( $P<0.001$ ) in patients with TT, and with ROLT it differed little from the control values. In addition, the absolute number of T-suppressors, as well as their percentage, was statistically significantly increased in patients of group 1 ( $P<0.001$ ), and decreased in patients of group 2 compared with the control values. With TT and ROLT, this indicator increased 1.6 and 1.9 times, respectively, which indicates the development of autoimmune processes in the body.

An imbalance of T-helpers and T-suppressors was revealed, which was accompanied by a sharp stimulation of the helper subpopulation in both forms, and against this background, there was a significant increase in T-suppressors in ASLT and a decrease in ROLT. When assessing changes in the humoral link of immunity in patients with ASLT, a significant increase in B-lymphocytes was revealed, compared with the control values by 1.3 times with TT and 1.5 times with ROLT. A similar pattern was observed in percentage terms in both groups.

A decrease in IgA and IgG levels, a slight decrease in IgM levels, and an increase in total IgE levels are detected in the blood of sick children. The highest IgE level was observed in the group of children with ROLT ( $362.0\pm19.5$  IU/l), which significantly exceeded the value of this indicator in children with TT ( $308.0\pm13.5$  IU/l) ( $P<0.05$ ) and in the control group ( $103.0\pm6.12$  IU/l) ( $P<0.001$ ). We noted that the content of immunoglobulins IdA, IgM and IgG in both groups was lower than the age-related parameters. In the group with recurrent croup, the level of total IgE was 2.5 times higher than in the case of TT, which indicates the role of the allergic factor in the pathogenesis of ROLT.

At the same time, in children with a recurrent course of the disease, the level of total IgE in all age groups exceeded the standard values, which not only confirms the presence of an allergic component of inflammation in the pathogenesis of the disease in a recurrent course, but also allows us to further clarify the content and focus of anti-relapse measures.

Changes in immunological parameters in patients with ASLT are associated with dysregulation of immunogenesis. To date, the issues of the functional state of the immune system in this category of patients remain insufficiently studied. The study of these issues is of both scientific and practical interest, as its ultimate goal is not only to discover certain patterns of development of the immune system in children with ASLT, but also a differentiated approach to their treatment in terms of increasing effectiveness.

According to the theory of polarization of the immune response, T-helper lymphocytes are responsible for the development of cellular immunity, and B-helper lymphocytes are responsible

for humoral immunity. Cytokines play the main role in regulating the type of immune response and in the realization of reciprocal relationships between them: tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ),  $\gamma$ -interferon (INF- $\gamma$ ), interleukins IL-1b, IL-4. To establish the role of the cytokine spectrum in the development of primary and recurrent ASLT in children, we determined the level of interferons IFN- $\alpha$  and IFN- $\gamma$ , the level of IL-4 and the level of proinflammatory cytokines: IL-1b, IL-6.

The data obtained by us show a reliable dependence of the concentration of the level of proinflammatory cytokines in the blood serum on the form of ASLT. Especially pronounced disorders are noted in children with ROLT. The revealed changes significantly differed from the values obtained in the group of infants. Thus, if the serum TNF- $\alpha$  level in the examined children was significantly exceeded with ROLT ( $243.5 \pm 23.9$  pg/ml compared with the data of the control group children –  $82.4 \pm 7.0$  pg/ml,  $P < 0.001$ ), then only a moderate increase in this cytokine was noted with TT ( $118.7 \pm 9.3$  pg/ml, compared with the control,  $P < 0.05$ ).

When analyzing the results of the study of the level of IL-1b in blood serum, it was revealed that in children with ROLT there was an almost tenfold increase in its level compared to the control –  $346.7 \pm 36.6$  pg/ml, versus  $35.8 \pm 3.9$  pg/ml ( $P < 0.001$ ). In children with PT, there was an increase in the level of IL-1b by more than 3 times compared with the control group of children –  $110.4 \pm 8.3$  pg/ml ( $P < 0.001$ ). As is known, IFN- $\gamma$  is produced by activated Th1 cells and NK cells. In our studies, the level of IFN- $\gamma$  was lower than in the control group of children. Moreover, this decrease is observed in ASLT: with ROLT –  $74.3 \pm 4.9$  pg/ml ( $P < 0.001$ ), with TT –  $78.5 \pm 7.3$  pg/ml ( $P < 0.001$ ). The level of INF- $\gamma$  in the control group of children averaged  $131.7 \pm 11.0$  pg/ml.

Thus, when analyzing the level of a number of inflammatory cytokines in the blood serum of children with ASLT, compared with controls, we noted a significant significant increase in the levels of TNFa and IL-1b with ROLT and a moderate increase in their serum levels with TT. The serum level of IFN- $\gamma$  in ASLT was significantly lower than in the control group and did not depend on its form.

ASLT is characterized by predominant activation of type II T-lymphocytes. The main cytokine responsible for the immune response along the Th2 pathway is interleukin-4, which, together with IL-12 and the CD40-CD40L molecular complex, is involved in triggering the synthesis of antigen-specific immunoglobulins of class E (IgE) by B lymphocytes. It has been established that the allergic process causes the activation of Th2-helper cells and the synthesis of cytokines, which have a suppressive effect on cellular immunity. The cytotoxic mechanism of damage, which is associated with T-killers, is activated. Consequently, our results indicate a violation of metabolic processes and pronounced immunological shifts that contribute to the development of complications of this disease.

Thus, the conducted immunological studies in the midst of ASLT in children indicate the development of immunological insufficiency of both cellular and humoral levels. It should be noted that the inflammatory process in the larynx leads to a decrease in immunological parameters, and the allergic background activates T-lymphocytes, which explains the imbalance of immunological parameters. And all this indicates the involvement of not only the inflammatory process, but also the allergization of the body of sick children. The immunological changes we noted can be classified as a secondary immunodeficiency condition.

Thus, we have studied the role of specific and non-specific immune defense factors in the pathogenesis of acute stenosing laryngotracheitis. The results show that in patients of both groups, the absolute number of leukocytes and lymphocytes in the peripheral blood increased statistically significantly ( $p < 0.001$ ). Thus, in patients with primary and recurrent laryngotracheitis, the number of leukocytes increased by an average of 62.8%, and lymphocytes – by 75.2%. In patients of the 2nd group with ROLT, more pronounced changes were observed: the number of white blood cells increased by 2 times.

The pathological process in TT and ROLT was accompanied by compensatory stimulation of the cellular mechanisms of the immune system. Thus, the absolute number of total T-lymphocytes significantly increased 1.3-fold with TT and 1.7-fold with ROLT, and patients in both groups also showed a significant increase in the percentage of T-lymphocytes. There was a significant increase in the number of T-helper cells ( $p<0.001$ ) in patients with TT, and in ROLT it differed little from the control value. In addition, both the absolute and percentage number of T-suppressors in patients of the 1st group increased statistically significantly ( $p<0.001$ ), and decreased in patients of the 2nd group.

With TT and ROLT, the immunoregulatory index increased 1.6 and 1.9 times, respectively, indicating the development of autoimmune processes in the body. A violation of the balance of T-helpers and T-suppressors was revealed, which was accompanied by a sharp stimulation of the helper subpopulation in both forms, and against this background, a significant increase in the number of T-suppressors was noted in ASLT, and a decrease in ROLT. The state of the humoral link of immunity in patients with ASLT was characterized by a significant increase in the number of B-lymphocytes compared with the control values by 1.3 times in case of TT and 1.5 times in case of ROLT. Similarly, the percentage of B-lymphocytes changed in patients of both groups. One of the most important characteristics of the B-immune system is the concentration of serum immunoglobulins. In patients with ASLT, the blood content of IgA, which is predominant in the immune complexes, exceeded the norm by 2.0-2.9 times.

The analysis of immunological parameters showed that in children at the height of the disease, compared with healthy children, the number of leukocytes, the absolute number of lymphocytes, T-lymphocytes, T-helper cells significantly decreases ( $p<0.05<0.001$ ) and the indicators of T-suppressors (CD8) and T-killers (CD16) significantly increase ( $p<0.001$ ). Taking into account the revealed changes in the immune status in patients with TT and ROLT, we considered it reasonable to include the immunocorrective drug Ergoferon in the complex therapy of children with ASLT.

Depending on the therapy, all patients were divided into 2 groups: group 1 – receiving traditional treatment; group 2 - receiving additional Ergoferon. Immunocorrective therapy with Ergoferon for children was prescribed according to age and in accordance with standardized treatment regimens. According to age and sex characteristics, the severity of the disease did not differ in the groups of patients. Drug tolerance in all children was good. There were no adverse reactions, including allergic ones, associated with the introduction of an immunocorrector. In addition, none of the children had an exacerbation of concomitant somatic pathology.

In patients with PTT, the duration of fever was slightly shorter when using Ergoferon compared with children receiving traditional treatment, and the symptoms of laryngotracheitis were relieved faster when treated with Ergoferon than in the control group. In children with a recurrent course of the disease, with the additional use of Ergoferon, the duration of fever averaged  $1.7 \pm 0.09$  days, and with traditional treatment, it averaged  $2.8 \pm 0.1$  days. The duration of laryngeal stenosis symptoms in patients receiving an immunocorrector decreased by 3 times compared with children in group 1. Productive cough with the effect of sputum dilution appeared against the background of Ergoferon treatment in combination with antibiotic therapy 2 times earlier than in children with traditional treatment.

In addition to evaluating the clinical efficacy of the drugs, we evaluated the restoration of immunoglobulin levels after treatment with an immunocorrector. In group 1, there was no significant difference in B-cell immunity in children with TT during treatment. In the group of ROLT patients receiving additional Ergoferon, IgM, Ig G and IgA levels increased by the end of treatment, approaching normal levels, and the IgE content in peripheral blood decreased.

The analysis showed the high effectiveness of the Ergoferon immunocorrector in ASLT, especially in its recurrent course. With ROLT, the fastest resolution of the symptoms of the disease: febrile, intoxicating and specific symptoms of laryngotracheitis was observed when

Ergoferon was included in complex therapy, which, apparently, is due to the mechanism of action of this drug. Our results showed that the combined therapy resulted in a more pronounced positive clinical result than in children who received traditional treatment.

**Conclusions.** In children with ASLT, especially with its recurrent course, significant features of the clinical picture of the disease were revealed, consisting in the predominant disease of boys aged 1-3 years (46.9%), more distal lesions of the respiratory tract in the form of laryngotracheitis (68.8%) and laryngotracheobronchitis (28.1%). In children with ASLT, suppression of cellular and activation of humoral links of immunity were revealed. The revealed significant changes in the immune status and cytokine link in patients with frequent relapses of ASLT were manifested by a significant increase in IL-4 and IL-1b levels, as well as an imbalance of interferogenesis and an increase in IgE levels. The use of an immunomodulatory drug with antiviral activity "Ergoferon" in the complex therapy of children with ASLT, especially with its recurrent course, has a beneficial effect on the clinical course of the disease, as well as on the indicators of the immune status of patients.

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