IMMUNOLOGICAL INDICATORS IN STENOSING LARINGOTRACHEITIS IN CHILDREN

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Abstract. *The modern concept of the etiopathogenesis of laryngotracheitis takes into account the action of multiple infectious and allergic trigger factors, which are most significant in immunocompromised children. We conducted a comprehensive examination and dynamic observation of 95 children with different variants of ASLT, which were divided into 2 groups. ASLT in children revealed suppression of cellular and activation of humoral immunity. Significant changes in the immune status and cytokine level in patients with frequent relapses of ASLT were manifested by a significant increase in the levels of IL-4 and IL-1β, as well as an imbalance in interferon genesis and an increase in the level of IgE.*

Keywords: *acute stenosing laryngotracheitis (ASLT), immunology, pathogenesis, children, recurrent course of acute laryngotracheitis (RASLT), primary acute laryngotracheitis (PASLT).*

Relevance. Acute infectious and inflammatory processes in the upper respiratory tract still form the main list of diseases in childhood, which maintains the constant interest of specialists in various fields in this pathology [1,2,8,14]. Particular attention of researchers and clinicians is attracted to the study of etiopathogenetic mechanisms of acute stenotic laryngotracheitis (ASLT), which is caused, first of all, by the development of a life-threatening condition of acute airway stenosis in children [3,4,10,11,12]. According to our observations and literature data, a clear trend towards an increase in the frequency of repeated episodes of ASLT in children has recently been noted, which makes obvious the need for further study of the underlying mechanisms of not only the occurrence, but also the recurrence of ASLT [1,6,7,9].

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 [4,5,10]. 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 [2,6,11].

The modern concept of the etiopathogenesis of laryngotracheitis takes into account the action of multiple infectious and allergic trigger factors, which are most significant in immunocompromised children [3,4,12]. However, to date, the role of cytokine regulation in the pathogenesis of the disease remains insufficiently studied; the diagnostic and prognostic value of

determining cytokine spectrum indicators for the occurrence and recurrence of ASLT in children has not been clarified [3,13].

Purpose of work. Study of the state of cellular and humoral immunity in acute and recurrent laryngotracheitis in children.

Material and research methods. To achieve this goal, a comprehensive examination and dynamic observation of 95 children with various variants of the course of ASLT was carried out. All patients were divided into 2 groups: children with a single episode of acute laryngotracheitis (63 patients with primary acute laryngotracheitis - PASLT) and with a recurrent course of acute laryngotracheitis (RASLT - 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, we used an additional examination, including determination of the cellular and humoral immunity (immunoglobulins IgE, IgM, IgG and IgA) in the blood serum, determination of the level of cytokines (IL-2, IL-4) before and after treatment with an immunocorrective drug , IL-6, IFN-α, IFN-γ) in peripheral blood.

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

Table 1.

Indicators of T-cell immunity in children with ASLT

Indicators	Control group (n=30)	1 group PASLT (n=63)	2 group RASLT (n=32)
Leukocytes, (g/l)	7080±216,9	9546±197,2***	8210±117,4***^^^
Lymphocytes, %	32,9±0,80	55,2±1,14***	57,0±0,86***
Lymphocytes, abs.	2344±104,6	5233±144,3***	4697±102,9***^^
CD3, %	60,9±1,82	61,7±1,28	66,3±0,86
CD3, abs.	1425±80,1	3241±114,6***	2920±75,0***^
CD4, %	38,7±1,09	35,1±0,77**	36,6±0,49
CD4, abs.	897±42,7	1838±66,5***	1726±46,3***
CD8, %	33,3±0,94	23,2±0,50***	21,5±0,31***^^
CD8, abs.	778±40,5	1214±43,7***	1006±25,4***^^^
CD_4/CD_8	1,20±0,05	1,61±0,05***	1,75±0,03***^
CD16, %	14,1±0,37	11,2±0,23***	9,9±0,13***^^^
CD16, abs.	333±18,3	592±22,5***	466±12,3***^^^

Note: * - differences relative to the control group data are significant (** - P<0.01, *** - P<0.001); ^ - differences relative to the data of group 1 are significant (^ - P<0,05, ^^ - P<0,01, ^^^ - P<0,001)

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 OSLT and a decrease in ROLT. When assessing changes in the humoral immunity in patients with OSLT, a significant increase in B-lymphocytes was revealed, compared with control values of 1.3 times in POSTRT and 1.5 times in ROSCLT. A similar picture was observed in percentage terms in both groups. In the blood of sick children, a decrease in the level of IgA and IgG, a slight decrease in the level of IgM, and an increase in the level of total IgE are detected. The highest level of IgE is observed in the group of children with RSLT (362.0±19.5 IU/l), which significantly exceeds the value of this indicator in children with POSTLT (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).

We noted that the content of immunoglobulins IgA, 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 POST-RT, which indicates the role of the allergic factor in the pathogenesis of POST. At the same time, in children with a recurrent course of the disease, the level of total IgE in all age groups exceeded the normative 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 makes it possible to further clarify the content and focus of anti-relapse measures.

Changes in immunological parameters in patients with OSLT 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, since the ultimate goal is not only to detect certain patterns of development of the immune system in children with OSLT, but also a differentiated approach to their treatment in terms of increasing efficiency.

According to the theory of polarization of the immune response, helper T lymphocytes are responsible for the development of cellular immunity, and helper B lymphocytes are responsible for humoral immunity. The main role in regulating the type of immune response and in the implementation of reciprocal relationships between them is played by cytokines: tumor necrosis factor-α (TNF-α), γ-interferon (INF-γ), interleukins IL-1β, IL-4. To establish the role of the cytokine spectrum in the development of the primary and recurrent course of 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 show a significant dependence of the concentration of proinflammatory cytokines in the blood serum on the form of ASLT. Particularly pronounced disorders were noted in children with RASLT. The identified changes were significantly different from the values obtained in the group of children PASLT. Thus, 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 during PASLT only a moderate increase in this cytokine was noted (118.7±9.3 pg/ml, compared with control P<0.05). When analyzing the results of a study of the level of IL-1β in the blood serum, it was revealed that in children with RASLT there is an almost tenfold increase in its level compared to the control - 346.7 ± 36.6 pg/ml, versus

35.8 ± 3.9 pg /ml (P<0.001). In children with PASLT, there was an increase in the level of IL-1β by more than 3 times compared to the control group of children - 110.4±8.3 pg/ml (P<0.001).
IFN-γ is known to be produced by activated Th1 cells and NK cells. Our studies showed a decreased level of IFN-γ compared to the control group of children. Moreover, this decrease is observed in ASLT: with RASLT – 74.3±4.9 pg/ml (P<0.001), with PASLT – 78.5±7.3 pg/ml (P<0.001). The level of IFN-γ, while in the control group of children, averaged 131.7±11.0 pg/ml. Thus, when analyzing the level of a number of inflammatory cytokines in the blood serum of children with ASLT compared to controls, we noted a significant significant increase in the level of TNFα and IL-1β during ASLT and a moderate increase in their serum content during PASLT. The serum level of IFN-γ in ASLT was significantly lower than in the control group and did not depend on its form.

ASLT is characterized by preferential 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 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 that have a suppressive effect on cellular immunity. The cytotoxic mechanism of damage, which is associated with T-killers, is activated. Consequently, our results indicate disruption of metabolic processes and pronounced immunological changes that contribute to the development of complications of this disease.

Immunological studies carried out at the height of ASLT in children indicate the development of immunological failure of both the cellular and humoral components. It should be noted that the inflammatory process in the larynx leads to a decrease in immunological parameters, and the present allergic background activates T-lymphocytes, which explains the imbalance of immunological parameters. And all this indicates the participation of not only the inflammatory process, but also allergization of the body of sick children. The immunological changes we noted can be qualified as a secondary immunodeficiency state.

Thus, we have studied the role of specific and nonspecific immune defense factors in the pathogenesis of acute stenosing laryngotracheitis. The results obtained show that in patients of both groups there was a statistically significant (p <0.001) increase in the absolute number of leukocytes and lymphocytes in the peripheral blood. Thus, in sick children with primary and recurrent laryngotracheitis, the number of leukocytes increased by an average of 62.8%, and lymphocytes by 75.2%. In patients of group 2 with RASLT, more pronounced changes were observed: the number of leukocytes in them increased by 2 times.

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

With PASLT and RASLT, the immunoregulatory index increased by 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, a significant increase in the number of T-suppressors was noted in ASLT, and their decrease in RASLT. The state of the humoral immunity in patients with ASLT was characterized by a significant increase in the number of B-lymphocytes, compared with control values by 1.3 times in PASLT and 1.5 times in RASLT. In the same way, 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 level of IgA, which predominates in immune complexes, was 2.0-2.9 times higher than normal. Analysis of immunological parameters showed that in children during the height of the disease, compared with healthy children, the number of leukocytes, the absolute number of lymphocytes, T-lymphocytes, T-helpers significantly decreases ($p<0.05<0.001$) and the indicators of T-suppressors significantly increase (CD8) and T-killers (CD16) ($p <0.001$).

Conclusion. ASLT in children revealed suppression of cellular immunity and activation of humoral immunity. The identified significant changes in the immune status and cytokine level in patients with frequent relapses of ASLT were manifested by a significant increase in the levels of IL-4 and IL-1β, as well as an imbalance of interferon genesis and an increase in the level of IgE.

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