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Research Article

The effect of immunomodulatory therapy with recombinant human interferon alpha-2β on blood cytokine levels in children with recurrent episodes of acute obstructive bronchitis

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Abstract

The high incidence of children with recurrent episodes of acute obstructive bronchitis is a widespread problem. Correct identification of children at risk of developing bronchial asthma at school age may improve treatment and prevention approaches to this pathology, but the ability to identify these children remains limited. The purpose of the study was to determine the effectiveness of recombinant interferon alpha-2β in children with recurrent episodes of acute obstructive bronchitis in the course of treatment based on the assessment of cytokine profile. The study examined 59 children of the main group with recurrent episodes of acute obstructive bronchitis and 30 children of the comparison group who suffered from acute bronchitis, aged 2–8 years, who were in the hospital. The results of laboratory studies were compared with the data of 30 healthy children. In children with recurrent episodes of acute obstructive bronchitis, the content of serum interferon-γ and interleukin-4 was significantly reduced compared to healthy children, after treatment with recombinant human interferon alpha-2β, the content of interferon-γ and interleukin-4 in children significantly increased. The content of interleukin-1β in children with recurrent episodes of acute obstructive bronchitis was significantly higher than in healthy children, after immunomodulatory therapy with recombinant interferon alpha-2β, interleukin-4 normalized to its level in healthy children. It was found that children with recurrent episodes of acute obstructive bronchitis have an imbalance of cytokines, the effectiveness of recombinant human interferon alpha-2β therapy, which normalized the levels of the studied cytokines in the serum.

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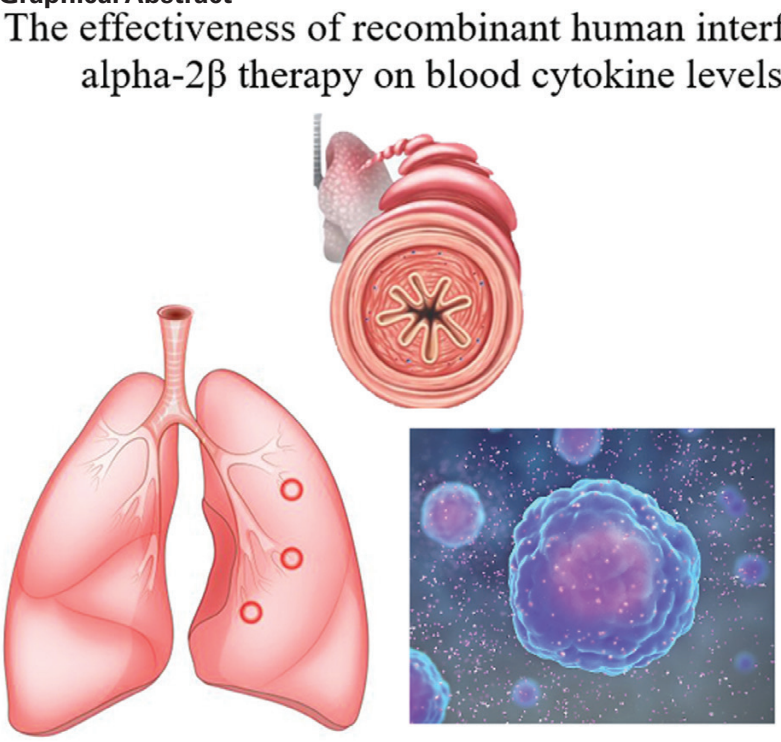
Graphical Abstract



Keywords: interferon-γ, interleukin-1β, interleukin-4, serum, inflammatory process

Abbreviations: AB: acute bronchitis; ABC: comparison group; AOB: acute obstructive bronchitis; ARD: acute respiratory diseases; HC: healthy children; IFN: interferon; IL: interleukin; M: values of the arithmetic mean; m: arithmetic mean error; *P*: degree of probability; *t*: Student's *t* test.

Introduction

Along with the high incidence of acute respiratory diseases (ARD), children who are often ill have a high incidence of acute obstructive bronchitis (AOB), which, according to various researchers, occurs in 10.0–30.0% of children with ARD, which significantly complicates treatment of such children in an outpatient setting. In addition, many patients in this group require inpatient treatment, which in turn is not only economically unprofitable for the state but also a stressful situation for both the child and their parents [1, 2]. As a determining factor in the development of recurrent episodes of AOB in children, bronchial hyperreactivity can be caused by various mechanisms: genetically determined, acquired due to chronic exposure to pollutants, viruses, bacteria, or due to impaired neuroendocrine regulation [3–7]. Despite the variety of factors that lead to recurrent episodes of AOB, the actual mechanisms of bronchial obstruction are well studied. Infectious factors are crucial in the development of the disease. The development of chronic inflammation is possible in early childhood under the influence of viruses on immature tissue structures. Against the background of ARD, bacterial inflammation often joins and the reproduction of microorganisms leads to further progression of inflammation conditioned by self-damage to the structure of the bronchus and due to activation of enzymes of inflamed cells [8].

The purpose of the study was to determine the effectiveness of recombinant interferon alpha-2β in children with recurrent episodes of AOB in the course of treatment based on the assessment of cytokine profile. The study hypothesis is to determine whether this immunomodulatory therapy can address the cytokine imbalance observed in these children and consequently improve treatment and prevention approaches for bronchial asthma at school age.

Objectives:

1. To determine whether recombinant interferon alpha-2β is effective in improving the cytokine profile of children with recurrent episodes of AOB.
2. To compare the cytokine profile of children with recurrent episodes of AOB to healthy children and those with acute bronchitis.
3. To investigate whether there is an imbalance of cytokines in children with recurrent episodes of AOB.
4. To evaluate the potential of recombinant interferon alpha-2β therapy in addressing the cytokine imbalance observed in children with recurrent episodes of AOB.
5. To provide insights into the identification, treatment, and prevention of bronchial asthma in children based on the assessment of cytokine profile.

Materials and methods

Study participants

The study examined 59 children of the main group aged 2–8 years, with recurrent episodes of AOB (I-AOB), who were hospitalized in the pulmonology and allergy department of the municipal non-profit enterprise of the Lviv Regional Council 'Lviv Regional Children's Clinical Hospital "OKHMATDYT"'. To compare the obtained data of children with recurrent episodes of AOB, a group of 30 children aged

2–8 years, suffering from acute bronchitis (AB) was selected no more than 1–2 times a year, which was a comparison group (II-ABC). Examination of this group of children was also conducted on the premises of the pulmonology and allergology department according to the same methodology as the examination of children in the main group. Verification of the diagnosis was carried out based on complaints from parents of sick children, anamnesis data, objective symptoms, and results of laboratory and clinical research methods, which were performed by the Order of the Ministry of Health of Ukraine No. 18 'On approval of Protocols for medical care for children in the specialty "children's pulmonology"' [9].

Research process

The results of laboratory tests were compared with data from 30 healthy children who were examined during expeditions of employees of the state institution Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine in ecologically clean areas of Lvivska Oblast and who, accordingly, were included in the control group of healthy children (III-HC). All patients underwent venous blood sampling for examination (4–5 ml) in the morning, on an empty stomach, and in a test tube without preservatives. The coagulation time in vitro did not exceed 30 minutes at a temperature of 2–25°C. After centrifugation for 10–15 minutes at 1500 rpm serum was collected, placed in sterile tubes and frozen (at –18°C) until the analysis procedure. Following the requirements of bioethics 'On laboratory research of biological material', the parents of each child signed written consent for the study of biomaterial.

All children underwent a general clinical examination, which included a study of primary medical records, history taking, paediatrician examination, chest X-ray, determination of O_2 saturation, and laboratory tests (clinical blood test, urine, and biochemical blood test). The levels of IL-1β, IL-4, IFN-γ in the serum of the subjects were determined by solid-phase enzyme-linked immunosorbent assay using the enzyme-linked immunosorbent assay 'Multiscan' using test systems produced by Vector-Best ZAO (Novosibirsk, Russia) according to the instructions. The study was performed in the acute period of the disease (on the 1-4th day of hospitalization and after 3 weeks). The clinical part of the study was performed on the premises of the pulmonology and allergy department of the municipal non-profit enterprise Lviv Regional Children's Clinical Hospital 'OKHMATDYT', laboratory tests were performed at the state institution Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine. The results were statistically processed on a personal computer using Microsoft Excel 7.0 software suite, calculating the values of the arithmetic mean (M), the arithmetic mean error (m), the Student's t test (t) and the degree of probability (P). Differences at $P < 0.01$ and $P < 0.05$ were considered statistically significant.

Results

Serum cytokines are used to measure the blood levels in children with recurrent episodes of AOB, because they are biomarkers of inflammation and immune response. Cytokines are signalling molecules that play a crucial role in regulating the immune response, inflammation, and tissue repair. In particular, interferon-γ and interleukin-4 are cytokines that are involved in the immune response against viral infections, which are a common cause of AOB in children.

The distribution of surveyed children by age and gender are presented in Table 1. Analysis of the data in Table 1 indicates that the comparative groups of children had no differences in the distribution by age and gender. The three groups of children had approximately the same number of boys and girls, aged 2–8.

Comparative analysis of the examined children with recurrent episodes of AOB and children with AB, who formed a comparison group according to clinical and radiological examination, and laboratory parameters, is presented in Table 2.

The general condition of children with recurrent episodes of AOB at the time of examination was assessed as moderate and severe. The condition of the children who made up the comparison group during the examination was assessed as satisfactory and moderate. Clinical manifestations of hypooxygenation were recorded in most children with recurrent episodes of AOB: pallor of the skin ($q = 0.66$ vs. 0.20 in the comparison group), decreased saturation ($q = 0.61$ vs. 0.00 in the comparison group), frequency of which probably differed from the data of the comparison group (Table 2). There was also a significantly higher frequency ($q = 0.92$ vs. 0.13 in the comparison group) of auscultatory changes in the lungs in the examined children with recurrent episodes of AOB (such as dry wheezing, shortness of breath, impaired breathing, etc.) compared to children in the AB group. The frequency of box percussion sound above the lungs in children of the main group with repeated episodes of AOB ($q = 0.86$ vs. 0.00 in the comparison group) was also high, which is conditioned by the presence of bronchial obstruction syndrome in these children, which is characterized by inflammatory changes in bronchi and narrowing of their lumen due to spasm.

In addition, a high frequency of radiological signs of obstructive bronchitis, such as compaction of the lung roots, thinning of the pulmonary pattern in the lateral lungs and thickening in the medial ($q = 0.75$ vs. 0.30 in children with AB). Changes in the blood test of children of the main group, such as eosinophilia ($q = 0.53$ vs. 0.13 in the comparison group) and lymphocytosis ($q = 0.58$ vs. 0.27 in the comparison group) were registered. Notably, cases of reduced oxygen saturation and percussion changes over the lungs in children with acute bronchitis were not registered at all (Table 2). Thus, the analysis of the results of the clinical examination and a set of clinical data found that in the anamnesis of sick children, there were at least 3–4 recurrent episodes of AOB per year, they were most often bothered by dry frequent cough, shortness of breath, fever, runny nose, and dry wheezing. At the next stage of the analysis of serum cytokines in children with

Table 1. Distribution of surveyed children by age and gender

Groups of children	Quantity, *n*	Age				Gender			
		2–5 years		6–8 years		Boys		Girls	
		n	%	*n*	%	*n*	%	*n*	%
I-AOB	59	39	66.0	20	34.0	34	58.0	25	42.0
II-ABC	30	18	60.0	12	40.0	16	53.0	14	47.0
III-HC	30	19	63.0	11	37.0	17	56.5	13	43.5

recurrent episodes of AOB in comparison with similar indicators in children with AB and healthy children. The results of the study on the content of interferon-γ, interleukin-1β, and interleukin-4 in the serum of children with recurrent episodes of AOB and children with AB in comparison with data from healthy children in the control group are presented in Table 3.

Serum interferon-γ content was significantly reduced in both children with recurrent episodes of AOB (7.116 ± 0.323 pg/ml) and in children with AB (8.114 ± 0.218 pg/ml) compared with healthy children (9.086 ± 0.219 pg/ml), significantly differing in the frequency of pathological signs. The study results showed that in children with recurrent episodes of AOB, there are significant disorders in the cytokine system (Table 3), which differed significantly from those of children with acute bronchitis in arithmetic mean and frequency of pathological signs, especially in content in the blood of interleukin-4. Thus, it was found that in patients of the first group during hospitalization, the content of proinflammatory interleukin-1β was significantly increased (3.396 ± 0.274 pg/ml) in comparison with the second and third groups of children (2.930 ± 0.329 pg/ml) and (2.742 ± 0.280 pg/ml), respectively, indicating the rapid development of a systemic inflammatory response in children with recurrent episodes of AOB [10]. The concentration of anti-inflammatory interleukin-4 was reduced 3 times in children with recurrent episodes of AOB (1.329 ± 0.232 pg/ml) and only two times in children with AB (1.894 ± 0.222 pg/ml) compared with healthy children (4.018 ± 0.411 pg/ml). Similar changes in cytokine status were observed by other researchers in periodontitis [11].

The follow-up revealed that the parents of 35 children followed the recommendation and that the children received a 5-day course of recombinant interferon alpha-2β at age doses rectally. And the parents of 24 children did not follow the recommendations and, accordingly, these children did not receive therapy with recombinant interferon alpha-2β. Three weeks after discharge from the hospital, all children were invited for a re-examination by a physician with a blood sample. Therefore, 3 weeks after administration of recombinant interferon alpha-2β, the serum levels of interferon-γ, interleukin-1β, and interleukin-4 were re-determined. The results of the study of serum cytokines in children with recurrent episodes of AOB in the dynamics of treatment with recombinant interferon alpha-2β and without it in comparison with data from healthy children are presented in Table 4.

The content of serum interferon-γ in children with recurrent episodes of AOB before treatment with recombinant interferon alpha-2β was significantly reduced (6.937 ± 0.362 pg/ml and 7.126 ± 0.294 pg/ml) in almost all children compared with its content in healthy children (9.086 ± 0.219 pg/ml). After treatment with recombinant interferon alpha-2β, the content of interferon-γ significantly increased, reaching the value of healthy children (8.765 ± 0.250 pg/ml) in 77.0% of subjects, while in children who did not receive Laferobion,

Table 2. Comparative analysis of the clinical condition of children with recurrent episodes of AOB with these children in the comparison group with AB

Clinical manifestations	Frequency of clinical and laboratory manifestations in groups of children			
	I-AOB		II-ABC	
	n = 59	*q*	*n* = 30	*q*
Pale skin	39	0.66*	6	0.20
Decreased saturation	36	0.61*	–	–
Auscultatory changes	54	0.92*	4	0.13
Box percussion sound	51	0.86*	–	–
Radiological signs of bronchitis	44	0.75*	9	0.30
Leukocytosis	16	0.27	10	0.33
Eosinophilia	31	0.53*	4	0.13
Lymphocytosis	34	0.58**	8	0.27

*Probable difference between the data of children with recurrent episodes of AOB and children of the comparison group, $P < 0.01$.
**Probable difference between the data of children with recurrent episodes of AOB and children of the comparison group, $P < 0.05$; q is the frequency of deviation of the parameter from the norm or from the reference value.

Table 3. The content of interferon-γ, interleukin-1β, and interleukin-4 in the serum of children with recurrent episodes of AOB and AB in comparison with data from healthy children, (M ± m)

Indicator	Groups of children:					
	I-AOB, *n* = 59		II-ABC, *n* = 30		III-HC, *n* = 30	
	M ± m, (pg/ml)	*q*	M ± m, (pg/ml)	*q*	M ± m, (pg/ml)	*q*
Interferon-γ	7.116 ± 0.323*	0.92*,**	8.114 ± 0.218	0.27*	9.086 ± 0.219	0.03
Interleukin-1β	3.396 ± 0.274*	0.76*,**	2.930 ± 0.329	0.33	2.742 ± 0.280	0.27
Interleukin-4	1.329 ± 0.232*,**	1.0*,**	1.894 ± 0.222*	0.63*	4.018 ± 0.411	0.33

*Probable difference between the data of children with bronchitis and healthy children, $P < 0.01$.
**Probable difference between the data of children with recurrent episodes of AOB and AB, $P_1 < 0.01$.

Table 4. Content of interferon-γ, interleukin-1β, and interleukin-4 in the serum of children with recurrent episodes of AOB in the dynamics of treatment with Laferobion and without it in comparison with data from healthy children (M ± m)

Groups of children		Indicators					
		Interferon-γ		Interleukin-1β		Interleukin-4	
		M ± m	*q*	M ± m	*q*	M ± m	*q*
Children with recurrent episodes of AOB, *n* = 59	Before treatment, *n* =35	6.937 ± 0.362*	0.91*,**	3.432 ± 0.332	0.77*,**	1.228 ± 0.26*	1.0*,**
	After treatment with Laferobion, *n* = 35	8.765 ± 0.250**	0.23*,**	2.503 ± 0.398**	0.40	2.986 ± 0.408**	0.63
	Before treatment, *n* = 24	7.128 ± 0.294*	0.88	3.297 ± 0.348*	0.75*,**	1.656 ± 0.24*	1.0*
	After treatment without Laferobion, *N* = 24	7.711 ± 0.290*,***	0.71***	2.953 ± 0.339	0.54***	2.079 ± 0.282*,***	0.92***
Healthy control, *n* = 30		9.086 ± 0.219	0.03	2.542 ± 0.380	0.27	4.018 ± 0.411	0.37

*Probable difference between the data of children with bronchitis and healthy children, $P < 0.01$.
**Probable difference between the data of children with bronchitis in the dynamics of treatment with Laferobion, $P < 0.01$.
***Probable difference between the data of children with bronchitis who received Laferobion and those who did not take it, $P < 0.01$.

the content of interferon-γ in the dynamics of treatment remained significantly reduced in almost all children (before treatment – 7.128 ± 0.294 pg/ml; after treatment – 7.711 ± 0.290 pg/ml, with its content in healthy children – 9.086 ± 0.219 pg/ml). Similar data were obtained in the study of blood levels of interleukin-1β and interleukin-4 in the examined children (Table 4). Notably, the data on the content of interferon-γ and interleukin-4 in the blood of children treated with recombinant human interferon alpha-2β and those who were not treated in the follow-up differed significantly ($P < 0.01$) (Table 4).

Discussion

Given all the above, the question arises as to the possibility of implementing an adequate cellular-type immune response in children with recurrent episodes of AOB, as such children mostly belong to the group of frequently ill children. According to the existing view, one of the key roles in the immune response, including regulatory, is assigned to the cytokine system [12]. Interferon-γ (IFN-γ) is a cytokine, a strong mediator of the immune response [13]. It belongs to type II interferons and plays an important role in preventing the development of infection, produced by T-lymphocytes and NK-cells (cells – natural killers) [11]. Interferon-γ is an activator of macrophage differentiation and a pro-inflammatory activator of innate immunity [6]. It has a number of pro- and anti-inflammatory properties [14–16]. Interleukin-1β (IL-1β) is a polypeptide proinflammatory cytokine with a molecular weight of 15 kD, which plays a leading role in the processes of acute and chronic inflammation, both local and systemic. It is secreted mainly by macrophages, T-lymphocytes, fibroblasts, and endotheliocytes [17, 18].

Interleukin-4 (IL-4) is a multifunctional anti-inflammatory cytokine of the interleukin group, which regulates the growth and differentiation of B-lymphocytes, the processes of biosynthesis, and the secretion of antibodies [19, 20]. It is produced by activated T lymphocytes (Th2 cells or type II T-helpers), mast cells, eosinophils, and basophils and plays an important role as a mediator and modulator of the immune and inflammatory response, having an immunosuppressive effect [21–23].

The cytokine network is a system that acts as a harmonious complex, capable of self-regulation, in which there is constant cooperation. The impact on any part of the cytokine network inevitably affects the functions of its other components [24, 25]. The state of the body's immune system depends on the balance of cytokine regulation. Synergism or antagonism in the process of cytokine interaction, depending on the situation, can lead to a predominance of cellular or humoral type of immune response. With the strengthening of cellular immunity, the humoral link will lead to normalization, thus achieving a functional balance between the immune system [26–28].

Analysis of the literature suggests that reduced levels of interleukin-4 stimulate the humoral (Th2) and inhibit the cellular (Th1) immune response. The data obtained indicate that the chronicity of the disease is accompanied by the activation of the Th2 type, which is associated with the synthesis of antibodies and the development of immunopathological manifestations [27, 29, 30]. The study showed that children with recurrent episodes of AOB have a more pronounced cytokine

profile imbalance than children with AB, caused by the impaired regulatory function of the immune system to therapy, according to the protocol for the treatment of AOB in such children (59 people) during convalescence, recombinant interferon alpha-2β (rectal suppositories) was administered on an outpatient basis in age-appropriate doses, twice daily, for 5 days [9].

According to the literature, recurrent ARD in children can cause hyperproduction of immunoglobulin E(IgE), decreased interferon-γ synthesis, which can lead to the development of bronchial hyperreactivity and sensitization of the child to non-infectious allergens [2, 31, 32].

Conclusion

Often, bronchial obstruction can be the first manifestation of various respiratory diseases and determines both the severity of the underlying disease and its prognosis. Bronchial obstruction that occurs against the background of ARD in children of the first three years of life is characterized by various diffuse bronchial lesions and is a predictor of a high risk of recurrent bronchial obstruction in subsequent episodes of ARDs and the development of bronchial hyperreactivity in pre-school and school age, which occurs in 15.0–30.0% of cases.

In children with recurrent episodes of AOB, the content of serum interferon-γ and interleukin-4 was significantly reduced compared to healthy children, after treatment with recombinant human interferon alpha-2β, the content of interferon-γ and interleukin-4 in children significantly increased, reaching the content in healthy children. The content of interleukin-1β in children with recurrent episodes of AOB was significantly higher than in healthy children, after immunomodulatory therapy with recombinant interferon alpha-2β interleukin-4 levels returned to normal in healthy children.

Based on the assessment of the cytokine profile, identifying children at risk of developing bronchial asthma at school age may improve treatment and prevention approaches to this pathology. The study's findings support the potential of recombinant interferon alpha-2β therapy in addressing cytokine imbalances observed in children with recurrent episodes of AOB and have implications for improving treatment and prevention approaches for bronchial asthma in children.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants (parents of sick children) provided their written informed consent to participate in this study.

Conflict of Interests

The authors declare no competing interest.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Author Contributions

T.K., N.L., D.K., V.D., and O.T. conceived and designed the work, performed the experiments, collected clinical data, performed the statistical analysis, and wrote the manuscript. All authors approved the final version of the article.

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