

THE ROLE OF IL6 GENE POLYMORPHISM –174C/G IN THE DEVELOPMENT OF RECURRENT BRONCHIAL OBSTRUCTION IN CHILDREN OF EARLY SCHOOL AGE

N. B. Sodikova¹  U. I. Zakirova¹  I. A. Karimjonov¹  U. N. Karimova¹ 

1. Tashkent Medical Academy1, Tashkent, Uzbekistan

OPEN ACCESS
IJSP

Correspondence

N. B. Sodikova

Tashkent Medical Academy,
Tashkent, Uzbekistan

e-mail: sadikovanozima7@gmail.com

Received: 09 March 2024

Revised: 13 March 2024


Accepted: 17 March 2024

Published: 29 March 2024

Funding source for publication:

Andijan state medical institute and I-EDU GROUP LLC.

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Abstract. The purpose of our work was to analyze the polymorphism of the IL6 gene –174C/G in the development of recurrent bronchitis in children of the Uzbek population of preschool age. **Material and methods.** To achieve this goal, 73 cases of the disease were analyzed, of which group 1 included children with acute obstructive bronchitis (AOB), group 2 - with recurrent bronchial obstruction (RBO) aged 7 to 11 years. Determination of IL-6 and total IgE in blood serum was carried out by enzyme-linked immunosorbent assay using a commercial kit of enzyme-linked immunosorbents. Total genomic DNA was isolated using the DNA-Express kit (Litekh). Single nucleotide polymorphism of the IL-6 gene 174G/C was determined by PCR. Statistical processing of the obtained data was carried out using Microsoft Excel 2013. Differences were considered statistically significant at $p < 0.05$. **Results.** A comparative analysis of IL6 and total IgE in AOB and RBO showed a significant increase in IL-6 and an increase in the level of IgE in RBO compared with the AOB group and healthy children. A study of the IL6 –174C/G gene polymorphism showed that the G/G mutacin genotype was observed significantly more often in the group of patients with RBO than in the healthy group. **Conclusion:** It follows that the main allele G is associated with an increased level of IL-6 expression and is a prognostic factor for the development of RBO in children. The obtained clinical, genetic and immunological results of the study allow us to predict RBR in children.

Key words: children, bronchitis, gene, cytokine, obstruction.

Today, one of the most common respiratory diseases in childhood is bronchitis, which is often accompanied by relapses and a protracted course. The high frequency of recurrent bronchial obstruction (RBO) in children of early and preschool age is due to both the morphofunctional characteristics of the respiratory tract in children of this age group and the high frequency of acute respiratory infections. Recurrent bronchitis with obstruction (RBO) has become widespread due to the difficulty of diagnosis, the ineffectiveness of anti-relapse treatment and an ambiguous prognosis. Prediction and proof of the existence of RBO in children allows one to avoid over diagnosis of bronchial asthma (BA) and provide a different approach to treating the disease and preventing its relapses, compared to bronchial asthma [1, 2, 6].

The study of immune pathological mechanisms in bronchopulmonary pathology in children is relevant for the analysis of pathogenetic mechanisms of the development of bronchopulmonary diseases. Cytokines, as low molecular weight protein substances, carry out endogenous regulation of intercellular interactions of all parts of the body's immune system. The development of RBO is also based on immune pathological mechanisms, which is accompanied by active infectious or allergic inflammation, leading to structural changes in the tissues of the lungs and bronchi. Cytokines, participating in the infectious-inflammatory process and allergic response at the level of a specific effective link, largely determine the direction, severity and outcome of bronchial obstruction [5,8].

Anti-inflammatory pro-cytokines play an important role in the development of many diseases in children. Urocytokine wave may indicate the onset of the disease, eth development AndExodus. Inflammatory processes occupy a leading place in recurrent diseases of the bronchopulmonary system. Determining the relationship between cytokine genes associated with single nucleotide polymorphisms (SNPs) and disease development is necessary to determine risk groups in children and make decisions on optimal therapy. IL-6 in the acute phase of the disease acts as both a pro-inflammatory and anti-inflammatory cytokine [3,4].

C the essence of our work: was the determination of the role of the IL6 gene polymorphism –174C/G in the development of recurrent bronchitis in children of early school age.

Materials and methods:

Material for research 73 patients served, of which group 1 consisted of 30 children with acute obstructive bronchitis (AOB) and 2 group-43 patients with recurrent bronchial

obstruction (RBO) in the Uzbek population aged 7 to 11 years. As a control group, 40 practically healthy children of the same age and population without broncho pulmonary pathology and allergic history were studied.

The examination of patients was carried out during the period of exacerbation of the disease, on the 2nd day of admission to the hospital. Children with AOB were patients who had bronchial obstruction syndrome (BOS) for the first time. Clinically, children with AOB were restless, which was accompanied by wheezing and prolongation of expiration, an unproductive cough was noted, and the temperature was high or moderate. The diagnosis of recurrent bronchitis occurring with bronchial obstruction syndrome (ROS) is made based on the presence of the following indicators: a history of at least 3 or more episodes of obstruction per year; the duration of the exacerbation episode is 2 weeks or more; presence of signs of bronchospasm, bronchial obstruction, respiratory failure; auscultator changes; the presence of prolonged cough and sputum; catarrh of the upper respiratory tract and increased body temperature. The diagnosis of AOB and recurrent bronchitis (RB) in children was established taking into account family and allergy history; clinical and laboratory data, in accordance with the "Classification of clinical forms of bronchopulmonary diseases in children", adopted at a symposium of pediatricians on improving the classification of nonspecific lung diseases in children [7]. All subjects underwent general clinical laboratory tests, specific blood tests, spirometry, X-ray examination of the chest and paranasal sinuses (as indicated), and electrocardiography.

Determination of IL-6 and total IgE in blood serum was carried out by enzyme-linked immunosorbent assay using a commercial enzyme-linked immunosorbent kit. Total genomic DNA was isolated using the DNA-Express kit (Litekh). Single nucleotide polymorphism of the IL-6 gene 174G/C was determined by PCR. Statistical processing of the obtained data was carried out using Microsoft Excel 2013. The differences were considered statistically significant at $p < 0.05$.

Research results

Our observations showed that out of 73 patients aged 7 to 11 years, of which group 1 consisted of 30 (41.1%) children with acute obstructive bronchitis (AOB) and group 2 - 43 (58.9%) patients with recurrent bronchial obstruction (BBO).

A comparative analysis of patients by age showed that among the subjects the majority were in the age category from 7 to 9 years (45.7%) (diagram No. 1). Cases of AOB were more observed in children under 7-8 years of age, while in the group with recurrent bronchial obstruction (RBO) - between the ages of 7 and 11 years.

The results of our observations showed that in children with AOB, most often the first signs of SBO appeared on the second or third day after the onset of a viral infection or after the child became hypothermic. We noted that relapses of SBO were more often observed in patients with a history of frequent ARVI, in particular 7 or more times a year, whereas in the healthy group the number of episodes was less than 3 times a year. Along with other studies by scientists and practitioners, our observations also showed that the early onset of SBO in children with acute bronchitis is an unfavorable sign for the formation of a recurrent course of obstructive bronchitis [1,6].

In the general group of patients, an analysis of the obstetric and somatic anamnesis of the mothers showed that most children were born from 1-2 pregnancies, while in 36.2% the pregnancy period was accompanied by anemia and 18.8% toxicosis. Also, mothers had previous abortions in 11.5% and medication use during pregnancy in 27.5%. Most of the observed children were born from full-term pregnancy, 8.6% of patients were premature, 4.3% of children were born with asphyxia. Among the risk factors in children with bronchitis, the presence of animals at home was found - 5.1%, dust - 10.8%, plant pollen - 13.7%, physical and emotional stress - 16.6%.

Often the course of AOB occurred against the background of rickets, anemia of 1-2 degrees, chronic nutritional disorder in the form of protein energy deficiency (PEM) grade 1-2 and paratrophy. In the vast majority of cases, RBO in children developed against the background of ARVI and was more often a manifestation of acute obstructive bronchitis. The research results showed that all patients with RBO had a history of 2-3 or more episodes of RBO within 1 year, with an exacerbation period of 1.5 weeks or more.

From the anamnesis, children with RBO and BA at an early age were noted to have constitutional anomalies in the form of exudative-catal diathesis and food allergies. Most often, the cause of PEM and anemia in children with bronchitis was nutritional factors: early transfer to artificial feeding, quantitative underfeeding (hypogalactia, taking insufficient amounts of formula) or qualitative underfeeding due to the poverty of the daily

diet in proteins, vitamins, microelements, as well as early transfer of children to artificial feeding and mixed feeding. The results of our study coincided with those of other authors, who argued that the anatomical and physiological characteristics of the respiratory tract, burdened premorbid background, and repeated infection of a child with a respiratory infection contribute to the recurrent course of bronchitis [2,6,9].

Thus, a careful collection of clinical and anamnestic data from the examined groups of children showed that endogenous factors in the development of bronchitis include anemia, paratrophy and food allergy. Analysis of the obstetric and somatic anamnesis of the mothers of the examined children showed that asphyxia during childbirth and prematurity are one of the risk factors for the development of RBD and BA in children. Among the exogenous risk factors for the development of bronchitis and asthma, frequent respiratory infections, blooms in the house and passive smoking are noted. With an early transition to artificial feeding, children significantly more often develop a recurrent course of SBO of both infectious and allergic origin. Apparently, this trend is due to the fact that premature weaning and transfer to artificial feeding contributes to early sensitization, expanding the range of potential food allergens, reducing the factors of passive humoral immunity, which, as a consequence, leads to the occurrence of repeated respiratory diseases [9, 10].

The results of studies of IL-6 and IgE in peripheral blood in children with bronchitis showed distinctive properties (Figure No. 1).

Table-1

Indicators of IL-6 and IgE in children with bronchitis (M ± m)

Indicators	OOB n=30 (41.1%)	RBO n=43(58.9%)	Control n=40	R
IL-6 pg/ml	21.41 ±1.24 pg/ml	36.27±8.16 pg/ml	11.32±0.72 pg/ml*	P<0.001; P<0.05
IgE IU/ml	48.31 ±5.45 IU/ml	90.17±6.38 IU/ml	46.21±5.41 IU/ml*	P<0.001

Note: * differences between patients and the healthy group (P<0.05), differences between the group with AOB, RBO ** (P<0.001).

P-statistically significant differences by Student's t test.

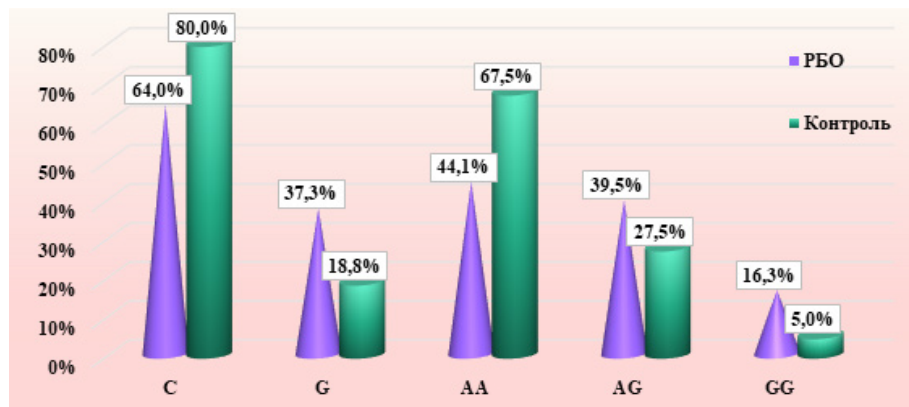
The IL-6 cytokine profile in all examined patients was determined during the period of exacerbation of the underlying disease. The research results showed a significant increase in IL-6 in the peripheral blood in children with bronchitis and RBO compared to the control group ($p < 0.005$). According to the study of pathogenetic mechanisms, the results prove the presence of an infectious genesis of inflammation in SBO in children. Analysis of the prevalence of IL-6 in the group of children with RBO averaged 36.27 pg/ml, while in the group of patients with AOB it was 21.41 pg/ml ($p < 0.001$). Perhaps a high level of IL-6 in children with RBO is associated with more frequent inflammatory processes occurring during the year, accompanied by a more severe course of RBO, which subsequently led to high bronchial hyperreactivity. As can be seen from the table, the level of IL-6 in RBO and AOB is significantly higher compared to the control group (21.41 pg/ml and 36.27 pg/ml versus 11.32 pg/ml).

Analysis of the level of total IgE in peripheral blood in the compared groups showed that in the group of children with RBO there was a significant increase in the indicator compared to the group with OOB (48.31 IU/ml versus 90.17 IU/ml; $p < 0.001$). A significant increase in IgE was observed in the groups with AOB and RBO patients relative to the norm and patients in the healthy group ($p < 0.001$). This once again proves the importance of the allergic component in the pathogenesis of the development of RBD in children. At the same time, in the group of children with ABO, IgE indicators were statistically lower than in the groups with RBO. ($p < 0.001$). This may be due to the fact that among children with AOB, the majority were children without an allergic component of inflammation.

We investigated the frequency distribution of alleles and genotypes of the IL6 gene polymorphism -174C/G allele rs 1800795 in the development of recurrent bronchial obstruction in children in the main group of patients with RBO $n=43$ (58.9%) and controls ($n=40$).

Figure-1

Frequency of distribution of alleles and genotypes of the IL6 gene -174C/G polymorphism in the patient and control groups



Note: * $p < 0.01$ - significant difference compared to the control group

According to the research results polymorphism of the IL6 gene $-174C/G$, the frequency of occurrence of the homozygous genotype A/A was noted significantly less often in the group of patients with RBO (44.1%) compared to the control group (67.5%) ($p < 0.01$). Heterozygous genotype A/G of the IL6 gene $-174C/G$ was observed more often in children with RBD (39.5%) compared to the control group (27.5%) ($p < 0.01$).

At the same time, the mutation genotype G/G of the IL6 gene $-174C/G$ is observed significantly more often in the group of patients with RBO than in healthy people (16.3% versus 5.0%, respectively $\chi^2 = 3.9$; $P = 0.05$; $RR = 3.8$; $OR = 4.4$; 95% $CI = 1.01-19.05$). It follows that carriers of the mutation genotype G/G polymorphism of the IL6 gene $-174C/G$ allele rs 1800795 are predictors of the development of the disease. Based on the data obtained, in the group of patients with RBO, there was a decrease in the proportion of the G/G genotype against the background of an increase in A/G genotypes. The frequency of the A/A allele in the control group was 67.5%, and in patients with RBO it was 44.1%. It follows that the major allele G is associated with increased levels of IL-6 expression and is a prognostic factor in the development of RBO in children. Also, an increased level of IL-6 in combination with an excess of IgE is a diagnostic criterion for BOS, and the most significant increase in their indicators is a prognostic marker for the formation of recurrent bronchial obstruction in children.

The features we have identified in children with bronchitis allow us to form risk groups and develop prognostic criteria for the development of the disease long before the manifestation of the disease and carry out early preventive measures. In this regard, further broad and comprehensive study of the pathogenetic mechanisms and immunological aspects of children's predisposition to the development of recurrent respiratory diseases is necessary.

CONCLUSIONS

1. A comparative analysis of IL-6 and total IgE in AOB and RBO showed a significant increase in IL-6 and an increase in the level of IgE in RBO compared with the AOB group and healthy children.

2. The above-mentioned clinical, anamnestic and immunological results of the study allow us to predict RBR in children. Clinical and anamnestic risk factors and a significant increase in IL-6 in combination with high IgE levels are unfavorable prognostic criteria for the formation of RBO in children.

3. A study of the IL6 gene polymorphism $-174C/G$ showed that the G/G mutacin genotype was observed significantly more often in the group of patients with RBO than in the group of healthy people. It follows that the main G allele is associated with an increased level of IL-6 expression and is a prognostic factor in the development of recurrent bronchial obstruction in children.

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