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Diterbitkan oleh

UMSIDA PRESS

Jl. Mojopahit 666 B Sidoarjo

ISBN: 978-623-464-096-0

УДК: 616.233-002-053.4

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Penulis: Sharipova Olia Askarovna;Bahronov Sherzod Samievich;drg.Tontowi Ashari
ISBN: 978-623-464-096-0
Editor: M.Tanzil Multazam,M.Kn & Mahardika Darmawan K.W,. M.Kn
Copy Editor: Wiwit Wahyu Wijayanti,S.H
Design Sampul dan Tata Letak: Wiwit Wahyu Wijayanti,S.H.

Penerbit: UMSIDA Press
Redaksi: Universitas Muhammadiyah Sidoarjo Jl. Mojopahit No 666B
Sidoarjo, Jawa Timur

Cetakan Pertama, Juni 2024

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Clinical and immunogenetic aspects of recurrent bronchitis in children with lymphatic-hypoplastic diathesis.” Monograph. Tashkent, 2024.-106 p.

The monograph summarizes literature data and long-term research by the team of the Department of Pediatrics and Medical Genetics of Samarkand State Medical University, devoted to the issues of diagnosis, clinic, treatment tactics, rehabilitation of patients with recurrent bronchitis. The stages and methods of diagnostic search and treatment tactics for recurrent bronchitis in children are described in detail and consistently. The monograph is intended for pediatricians, surgeons, and general practitioners.

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LIST OF SYMBOLS

ACTH - adrenocorticotropic hormone

RD - respiratory diseases

DNA - deoxyribonucleic acid

IL (IL) - interleukins

K - control group

LHD - lymphatic-hypoplastic diathesis

RB - recurrent bronchitis

STH - somatotropic hormone

PCR - polymerase chain reaction

EDTA - ethylenediaminetetraacetic acid

Ig – immunoglobulin

OR - odds ratio RR - risk of developing

TNFα - tumor necrosis factor

TREC - T-receptor excision rings

SNP - single nucleotide polymorphism

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PREFACE

In recent years, in all developed countries of the world, in the structure of general morbidity, pathology of the bronchopulmonary system in children has increased 3.6 times, mainly due to the acute and recurrent inflammatory nature of diseases of the lower respiratory tract. Today, it is recurrent bronchitis in children that is widely discussed by pediatric pulmonologists and is the focus of attention of scientists and practitioners.

On a global scale, special attention is paid to scientific research into the etiology, mechanisms of development, diagnosis, differential diagnosis, the course of childhood diseases, in particular recurrent bronchitis, as well as effective methods of treatment and prevention. In this regard, timely diagnosis of recurrent bronchitis in children, determination of factors contributing to the development of this disease, assessment of immune and hormonal status, determination of the role of pro- and anti-inflammatory cytokines on the course of RB, identification by correlation analysis of the features of the relationship between the polymorphism of cytokine genes and their content serum levels for recurrent bronchitis in children with lymphatic-hypoplastic diathesis are a priority.

This monograph is devoted specifically to this section of childhood pulmonology, the coverage of which is of great practical importance.

The monograph, along with materials from our own observations, widely summarizes literature data regarding recurrent bronchitis in children. The team of authors of the monograph expresses the hope that the materials contained in it will be of clinical interest to a wide range of pediatricians.

Chapter I. MODERN ASPECTS OF THE UPGROWING PERIODIC RECURRENT BRONCHITIS IN CHILDREN WITH STRUCTURAL ANOMALIES AND PROFYLAXIS OF THIS GROUP OF CHILDREN

1.1 Recurrent bronchitis as a multifactorial pathology

One of the most common lesions of the lower respiratory tract is bronchitis, including recurrent bronchitis, which ranks second in the structure of morbidity in childhood after acute diseases of the upper respiratory tract with an average increase of 1‰ per year [19,67,69,147].

Repeated episodes of bronchitis in children increase the risk of reduced respiratory function and bronchial hyperresponsiveness, creating conditions for the implementation of a generalized reaction and increased sensitivity of the bronchi and the processing of chronic types of bronchopulmonary disorders. [6,10, 32, 107,159].

According to Yu.G. Antipkin [5], the risk group for the formation of chronic bronchitis are children with recurrent lower respiratory tract infections, namely with RB.

As mentioned above, the relevance of the problem of respiratory diseases is determined by the prevalence of respiratory diseases in the structure.

The frequency of occurrence of RB in Ukraine according to Antipkin Yu. G. et al. [5] is 2.5 per 1000 children aged 1-15 years and the detection rate among preschool children is 7.1% [5]. Also, a number of other researchers point to the high prevalence of RB in the structure of childhood morbidity [60, 93]. Thus, at the age of 3- 7years it is increased 5-6 times, reaching 250 cases per 1000 children in environmentally unfavorable areas [59, 159].

Observations of Tatochenko V.K. [93] showed that the incidence of RB in different clinics ranges from 1.8 to 3.7 per 1000 children aged 1-15 years. Among all the considered bronchopulmonary pathologies, the proportion of RB is 34.3% in children 2-3 years old, 23.6% in children 4-6 years old, 25.7% in children 7-9 years old, 4-6 years old. It was 13.5%. For children from 10 years old.

The prevalence of recurrent bronchitis (RB) in the Russian Federation is 16.4 cases per 1000 children [93]. According to a number of authors, out of 1000 children, 40-50 people aged 1-3 years, 75-100 people aged 4-6 years, 30-

40 people aged 7-9 years suffer from them. Pathology is higher in environmentally disadvantaged areas. [17, 60, 93].

In Uzbekistan, according to statistic data, in the complex of common morbidity, respiratory diseases account for 24 per 100,000 population, and are diagnosed for the first time [169].

In ICD-10, the diagnosis of RB is not presented as a nosological unit, but RB remains in this classification. Currently, in many countries it is generally accepted that it begins in childhood [5].

According to the classification of clinical forms of bronchopulmonary diseases in children adopted in the Russian Federation, recurrent bronchitis belongs to category J 40 [178].

According to this classification, recurrent bronchitis is bronchitis without obstruction, the episodes of which are repeated 2-3 times over 1-2 years against the background of acute respiratory viral infections. Episodes of bronchitis are characterized by a duration of clinical manifestations of 2 weeks or more [32,43, 75,92].

Clinical and radiological manifestations during the disease period correspond to the signs of acute bronchitis [10, 84,103, 93]. A significant proportion (54%) of children with RB experience recurrent episodes of obstructive syndrome due to increased bronchial hyperreactivity [147]. According to the literature, the frequency of obvious clinical signs of bronchial obstruction in RB is 70–80% [17,23,58,84,153].

In young children with respiratory infectious diseases, the process more often affects the lower respiratory tract with the development of broncho-obstructive syndrome, which determines the severity of the child's condition and often leads to hospitalization [75, 102, 147].

The great interest of many scientists in the problem of recurrent bronchitis is associated not only with the high incidence of this pathology in children, but also with a number of controversial issues related to classification, difficulties of differential diagnosis and the possibility of transformation into other bronchitis. In nosologically forms at later stages of life [5, 59, 116].

Today, to make a diagnosis of RB, a thorough history is taken, an objective assessment of clinical data, and modern methods of instrumental and laboratory diagnostics are used, which make it possible to correctly make a

clinical diagnosis and develop an individual treatment and prevention plan [178].

In foreign literature, relapses include acute exacerbations of bronchitis that are repeated throughout the year, especially in preschool children [59,83].

It is known that RB does not cause irreversible dysfunction of the respiratory system. However, in a certain group of children, chronic infectious-inflammatory, allergic diseases, congenital and hereditary lung diseases can be classified under the name of recurrent bronchitis [103,178].

The modern classification emphasizes that RB occurs, as a rule, in children in the first 4-5 years of life. According to other authors, this nosology is most often registered under the age of 7 years [19,79,84].

According to the modern classification, RB usually occurs in children during the first 4-5 years of life. According to other authors, this nosology is registered up to 7 years of age [19,79,84].

As is known, age restrictions are based on the properties of the respiratory and immune systems, which are mainly associated with the processes of their development and protection. According to the literature, in the first years of a child's life, processes of intensive growth and differentiation of elements of lung tissue and the active formation of local immunity occur, which are considered completed by 6-7 years [6, 24, 93,106,109].

Numerous publications on the problem of RB do not answer a number of important questions about the cause of this disease, etiopathogenetic and clinical aspects.

Research in recent years shows that the occurrence of RB is closely related to acute respiratory viral infection, when the provoking factor for the development of the first episode of recurrent bronchitis is influenza virus or parainfluenza type 1, adenovirus and respiratory syncytial virus. In this case, a bacterial infection can be combined with repeated exacerbations of bronchitis [45, 96, 159]. Also, there is evidence that recurrent obstruction in RB depends on the existing individual characteristics of the reactivity of the children's body and, under the influence of a respiratory infection, can transform into bronchial asthma [23, 62, 98,134].

Predisposing factors to the occurrence of obstruction in RB, in all young children, are hyperplasia of glandular tissue, hypersecretion of mucus, relatively thick, loose, hyperreactive bronchial mucosa and relative narrowness

of the airways [79,153]. According to the literature, the frequency of pronounced clinical signs of bronchial obstruction in recurrent bronchitis is 70-80% [60,79, 83,103

Recent work has shown that respiratory viruses can provoke the development of transient bronchial hyperactivity within 4-6 weeks from the onset of the disease due to irritation of the nerve endings of the submucosal layer of the bronchi [64, 65].

One of the most common clinical manifestations of recurrent bronchitis (RB) remains a high cough readiness in children, the mechanisms of which are poorly understood and fragmentarily covered [6, 64,68,108].

Data from N.S. Pobedinskaya [67] indicates that the emerging hypersensitivity of the bronchi in children with recurrent bronchitis is one of the pathogenetic mechanisms of the persistent course of inflammatory changes in the bronchi and increased cough readiness. According to numerous studies, RD in children of early and preschool age often occurs under the influence of unfavorable environmental factors [1, 63, 65, 93, 103].

A number of researchers have pointed out the role of hereditary and allergology history, as well as the presence of concomitant ENT pathology and other foci of chronic infection, thymomegaly in the development of RB in children [63,69, 93, 103].

Ante- and perinatal factors are considered important in the development of RB. Infants born to mothers with preeclampsia, hypertension, and diabetes are at increased risk of early transient and persistent obstruction, and antibiotic use during labor can cause both early transient and persistent obstruction [1,41,63,78,88].

There are studies on the influence of passive smoking, pollution outside and inside the home air and poor material and living conditions on the development of RD in children [60,92]. In addition, the significance of perinatal factors, such as the threat of miscarriage, previous stillbirths, intrauterine infection, etc., is discussed. [60,103, 178].

Visiting preschool institutions is essential for the development of the Republic of Belarus [59,159].

According to Savenkova N.D., Dzhmagaziev A.A., [159] in children with RD living under conditions of combined exposure to adverse anthropogenic factors in the Astrakhan region, there is an imbalance in the dynamics of the

main components of immunity, which manifests itself in suppressed immunity. T-cell immunity, decreased phagocyte activity, maintenance of high levels of anti-inflammatory cytokines (IL-1β, IL-6).

An important role in the predisposition to the formation of respiratory diseases in children is assigned to individual characteristics of reactivity, that is, constitutional anomalies [45, 65, 90,92].

The specificity of the course of respiratory diseases in children with an unfavorable premorbid background has been noted in a number of scientific studies, which confirms the high importance of the problem of comorbidity in clinical practice [4,31,79,81].

Among the predisposing factors leading to recurrent bronchitis (RB) in children, much attention is paid to the presence of background diseases and structural changes. Nevertheless, lymphatic-hypoplastic diathesis (LHD) has no small importance. This is a inherent abnormalities caused by inadequacy of the lymphatic system, related to decreased function of the thymus gland, impairment of the endocrine system, and for that reason, these children do not tolerate any infectious diseases adequately, furthermore, LHD generates a specific background against any disease could change its direction and clinical appearance [16, 90].

Thus, presented literature data indicate that the etiology and pathogenesis of RB is complex, not all of its links have been sufficiently studied, in addition, the literary sources do not cover the features of the clinical course of recurrent bronchitis in children with lymphatic-hypoplastic diathesis, although these children require special observation and vigilance during illness. Further research in this direction will allow optimizing the criteria for predicting the risk of RB in children with LHD. All this can serve as the basis for an adequate choice of treatment and prevention of RB against the background of LGD in the hospital and in the clinic.

1.2. Immunogenetic factors in the development of bronchopulmonary pathology in children

One of the specific results of learning the human genome is the disclosure and swiftly progressing of a narratively new field of medical science - biomolecular medicine [27,47, 55].

Uniqueness of the biomolecular medicine as a science according to information about the biomolecular composition of the human genome lies in its individual nature. It is aimed at correcting the pathological changes in a

particular person, according to its individual genome [12,70,88,104]. Eventually understanding of their function in the pathologic initiation of many diseases allows, in other ways, to anticipate the risk of progressing pathology or the seriousness of the disease, and, also, individually choose special therapy for a particular patient [1, 68]. Another important feature is the preventive focus, when further knowledges about human genome can be receive before the onset of the disease and its elimination [49, 70, 172].

The occurrence of respiratory diseases is then controlled by genetic polymorphisms of human resistance [66, 146, 171].

Also, we observed further role of genetic differentiation in various multifactorial pathological conditions of the modern economy. The combination of multiple unfavorable alleles with the presence of disease predisposing factors is likely to cause many diseases [83,101].

One of the most promising approaches to assessing genetic predisposition to many recurrent diseases, in particular respiratory diseases, is to identify their association with certain candidate genes [88,151, 170].

As is known, when studying genetic determinants, two main approaches are used: candidate and positional mapping. Using candidate mapping, associations or linkage of a disease with polymorphic variants of genes that are tightly associated to the development of the pathology under study are analyzed [25, 141, 148].

Based on modern data on the pathogenesis of respiratory tract damage, genes for pro- and anti-inflammatory cytokines are one of these candidate genes [40, 42, 95,117,119]. Knowledge of their existence in the pathologic observation in many diseases enables to predict the risk of developing morbidity or the seriousness of the particular diseases, and, on the other hand, individually select specific therapy for a particular patient [30,70].

The mass of researchers contemplates cytokines as one of the important biomarkers of the inflammatory response of the respiratory system [15, 33,34,86,142]. Today, cytokines have been identified as a new independent system for regulating the fundamental functions of the body, accompanied with central nervous and endocrine, as well as regulatory systems. They has specifically leading role in assigned to maintaining homeostasis during the disruption and swallowing of the tissue integrity [12, 87,123].

Cytokines have a number of common biochemical and functional characteristics that distinguish them from other classes of regulatory

molecules. Currently, more than 200 individual substances belonging to the cytokine family are known [34,39, 99, 94].

The expression of cytokine genes begins in response to the penetration of pathogens into the body, antigenic irritation, or tissue damage. [91, 51].

It also acknowledged [49] that the potency of cytokine producing is determined genetically. Polymorphism of various cytokine genes has been described, and the number of polymorphic regions in the gene can be in the dozens [12]. They are detected in the coding regions of the exons of the gene, and also in the non-coding introns and, most importantly, in the promoter regions of the gene. In particular DNA sections regulate the amount of the protein component [68]. It has been shown that variants of cytokine genes are associated with a predisposition to many diseases, the characteristics and severity of their course, as well as an increase or decrease in the number of produced cytokines [37,91].

The biologically active form of IL-1β, a protein with a molecular weight of 17 kJ, is formed from a large (31 kJ) inactive precursor pro IL-1β and is strictly controlled at several levels. [57, 122, 123].

The IL-4 gene is located on the extended arm of 5th chromosome and consists of 4 exons. The IL-4 gene is also characterized by genetic polymorphism. The most significant is rs2243250 (C589T). For the IL-4 rs2243250 gene, increased transcription factor binding in the existing of the polymorphic T allele was shown [12, 101, 135, 137]. Increased IL-4 activity associated with rs2243250 has also been demonstrated [12, 101].

There is evidence in the literature that individuals who carry T alleles for IL-4 in higher risk of developing COPD [3, 13,78]. Against this study, Shang H. et al. [161] it was shown that the rs2243250 polymorphism is not related with the development of this disease.

The cytogenetic locus of IL-6 is 7p15.3. Several nucleotide polymorphisms have been found in the coding chain of the IL-6 gene in addition in the promoter region. One of the most popular and researched is rs1800795 (G174C). It is specified by the appearance of cytosine (C) at position 174 of the promoter instead of guanine (G). Homozygous carriers of the wild-type G allele exhibit an increase in IL-6 concentrations [94, 125, 173].

The IL-10 gene is localized at locus 1q32.1. There are currently about 194 polymorphisms in the gene. However, the most significant is rs1800896 (A1082 G) [30,128, 132].

The attendance of the variant G allele is connected with high IL-10 synthesis, whereas the A allele results in decreased IL-10 production in vitro [74,76,115,166]. The frequency of the G allele in the European population reaches 30%.

Currently, the polymorphism of the TNF-α gene has been widely studied. The TNF-α gene is described on the short arm of chromosome 6 and 43 polymorphisms have been identified, 9 of which are associated with malignant neoplasms, diseases of the cardiovascular system and respiratory tract, differing in etiology, course and prognosis [52, 82, 124, 136, 143].

It was identified that the homozygous genotype TNF-α, (-308A/G) expanded the relative risk of enveloped chronic respiratory diseases with AA alleles by 6.4 times and GG alleles by 2.4 times, while the heterozygous genotype (AG) reduces this risk 1.9 times [47].

As a consequence of allele A of the G308A polymorphism, the expression of the TNF-α gene increases tens of times, which under certain conditions can affect the body's immune reactions with the formation of systemic manifestations of the inflammatory process, up to septic shock [34, 52,76, 145,164].

A study conducted by O.I. Pikuza et al. [66] showed an increase in the frequency of the TNF-α (-308) A\A genotypes in patients with acute obstructive bronchitis and with a tendency to chronicity of the disease, which is contemplated as marker of higher risk of the disease. At the same time, the researcher noted a downward in the frequency of the genotype (-308) A\G, which was classified as protective (OR=0.26, 95% CI [0.22-0.70] and regarded this as a reduced risk of developing acute bronchitis. B At the same time, when studying the frequency distribution of alleles and genotypes (-174) C/G of the IL-6 gene and the +3953 C/T polymorphism of the IL-1β gene, the authors did not find significant differences with the control.

The expression and production of TNF-α and many cytokines is regulated by exchanging and polymorphisms (single nucleotide polymorphism SNP) of its genes, rely upon localization in the promoter or its structural part [12].

The result of polymorphism of regulatory locus of cytokine genes depends on the amount of secreted protein has been studied by a number of authors [12].

According to Rizvanov, F.F. et al. [70] and Sovalkin V.I. et al. [166] polymorphism of the TNF-α, IL-6 and IL-8 genes influences the structure of

the inflammatory action. At the same time, the authors find out two polymorphic regions with single-nucleotide substitutions that affect the amount of the synthesized product: -308 (G-A) and 238 (G-A).

Research Stashkevich D.S. [91] variations in innate immune reaction genes such as TNF-α-863A, TNF-α 376G, TNF-α 238G, IL-10-1082A and IL6-174G alleles in promoter sequences can lead to changes in cytokine production, which brings about change in the inflammatory response and, therefore, contributes to the emergence of a predisposition to otitis media.

Information about the function of this mutation in the advancing of chronic suppurative otitis media was analyzed by E.V. Baike. et al. [8]. The authors found that the most significant genotypes in the arranging of susceptibility to the development of the disease are C/C polymorphisms C3953T and T31C of the IL-1β gene, A/A polymorphism G1082A and TT polymorphism C819T of the IL-10 gene. Polymorphic variants of the IL-1β genes (genotype C/C polymorphisms C3953T and T511C) and IL-10 (genotype A/A polymorphism G1082A) are combined with the onset of chronic purulent otitis media before the age of 14 years. Polymorphism C174G of the IL-6 gene does not have a predisposing effect on the development of the disease

According to Yi Hu [177,180], the polymorphic allele -308A of the TNF-α gene in tuberculosis infection is ambiguous and is more common among tuberculosis patients compared to normal people and risk factor for them occurrence and development of this disease.

Studying the relationship of allelic polymorphism of the TNF-α, IL-2, IFNG genes with changes in their secretion in patients with pulmonary tuberculosis depending on the clinical form Churina E.G. et al. [104] demonstrated that IL-2 hyposecretion is determined by the carriage of the G allele and the GG genotype (T-330G) of the IL-2 gene in tuberculosis patients, regardless of the clinical form. In patients with disseminated tuberculosis - carriers of the homozygous genotype TT (T-330G) of the IL-2 gene, increased protein secretion was determined. The maximum secretion of TNF-α was recorded in individuals with the AA(G-308A) genotype of the TNF-α gene, in the control group and in patients with infiltrative tuberculosis, while this genotype was absent in patients with disseminated tuberculosis.

Hyposecretion of this cytokine was determined in carriers of the homozygous GG genotype (G-308A) of the TNF-α gene in all studied groups. IFNG secretion was not affected by the polymorphism (+874A/T) of the IFNG gene, despite everything of the clinical sequence of the disease. Also research

by Balpanov G.T. [9] showed that the frequency of occurrence of the G allele and genotype GG(T-330) of the IL-2 gene, genotype TT (C-590) and genotype AA (G-308A) of the IL4 gene) of the TNF-α gene occurred significantly more often than with infiltrative pulmonary tuberculosis. The risk of developing pulmonary tuberculosis is associated with GG (T-330G) genotypes of the IL2 gene; CT and TT of the IL-4 gene (C-590T), AA of the IL-10 gene (C-592A); GA and AA of the TNF-α gene (G-308A).

In general, the authors came to the conclusion that the functional polymorphism of the genes of the proinflammatory cytokines TNF-α, IL-2, IFNG is a significant factor in the dysregulation of the secretory function of immunocompetent cells, and therefore may predispose not only to the development of tuberculosis, but also to its worsening and progression currents. According to HuGEN, [131] the C1031T, G308A, G238A, C857A, A1078G polymorphisms of the TNF-α gene are associated with bronchial asthma, and several studies have examined the association of the G308A polymorphisms of the TNF-α gene [130,155,157].

In residents of the UK, USA, Mexico, Korea, Japan, and Russia, the 308A allele is more often detected with asthma [77, 126,145,150, 152,158, 176].

Egyptians are characterized by AD associated with the G308 allele [180], while in China, according to four studies, AD alleles G and A of TNF-α are found in AD [179]. Also, research conducted by Muhammadieva G.F. et al. [55] consisted of studying possible associations of polymorphic alternatives rs1800629 of the TNF-α gene with the development of chronic bronchial asthma in residents of the Republic of Bashkortostan. The authors revealed a predominance of the G allele and the GG genotype. The homozygous AA genotype was not found in patients with asthma or in practically healthy individuals.

At the same time, there is information about the absence of an association of the G308\308A alleles of the TNF-α gene with AD [77].

In children with asthma living in Belarus, the frequency distributions of G308\308A alleles of the TNF-α gene did not differ significantly from those for healthy residents (0.853\0.147) [77].

Studies on the effect of genotypes and G308\308A polymorphisms of the TNF-α gene on the production of TNF-α in patients with AD are insignificant and contradictory.

So, Rudenko K.A. et al. [77] studied the prevalence of the G308|308A polymorphism of the TNF-α gene among residents of the Republic of Adygea and determined the multidirectional influence of the G308|308A polymorphism of the TNF-α gene on the level of TNF-α production in the studied groups. The authors found that the G308 allele and the GG genotype increase, and the 308A allele and the GA genotype decrease the stimulated production of TNF-α in patients with bronchial asthma compared with donors.

Studying the characteristic of polymorphism of the cytokine genes TNF-α G-308A, IL-10 C592A, IL-10 C819T, IL-10 G-1082A Romanova et al. [74] in patients with influenza complicated by pneumonia, found that homozygous carriers of the allele G polymorphism (308 G\A) of the TNF-α gene were more common. The authors regarded this as a cause of disturbances in immune defense mechanisms. The G allele of the IL-10 gene (1082G/A) and the C allele of the IL-10 gene (592C/A) also significantly predominated in patients, mainly in the form of homozygous carriers. The authors who studied the prevalence of allelic variants of the IL-10(819) C|T gene did not reveal differences in the study groups, and homozygous carriage of T\T was significantly higher in healthy individuals. The authors did not find a relationship between the severity of pneumonia and genotypes. Also, when studying the concentrations of the cytokine's TNF-α and IL-10 in the blood serum, no differences were revealed depending on the genetic variants of the studied polymorphisms.

There are also have been involved on the study of polymorphism of the IL-10 gene in newborns with intrauterine infections and purposely significant polymorphisms were found in the promoter region of the IL-10 gene at positions -592 A\C, -819 T\C, resulting from single nucleotide substitutions. The association established between single nucleotide substitutions in interleukin genes and the incidence of intrauterine infections helps to determine the risk group and genotypes of susceptibility to infections. [25].

A study conducted by Stashkevich D.S. et al. [91] showed that patients with COPD who are carriers of the A allele of the polymorphic locus G -308A of the TNF-α gene have an increased risk of developing coronary heart disease, while carriers of the T allele of the polymorphic locus C +3953T of the IL-1β gene have a risk of developing arterial hypertension. Statistical analysis carried out by Loskutov D.V. et al. [47] demonstrated that the frequency of occurrence of homozygous variants AA and GG of the TNF-α gene was higher among patients with chronic respiratory diseases, while in the group of healthy

individuals carriers of the heterozygous AG genotype predominated, which determined the body's resistance to the risk factor for the development of respiratory diseases . The writers did not reveal statistically remarkable differences were studying allelic variation of the IL-1β gene, which was interpreted as the not attendance of the IL-1β gene (+3953T/C) in the formation of respiratory diseases.

Assessing the risk of polymorphic types of the TNF-α, IL1 β cytokine genes in the evolution of hereditary proneness to respiratory disorders in newborns K.V. Danilko et al. [27] found that the IL-1β*-511T-IL-1β *3953T-IL1RN*A2 haplotype is associated with an increased risk of developing respiratory distress syndrome (RDS), and the IL-1β *-511T-1IL-1β *3953-haplotype IL1RN*A1- with reduced risk. In addition, markers of predisposition to the development of infectious complications in patients with RDS were found: the *A1 allele and the A1A1 genotype of the VNTR locus of the IL1RN gene. Allele IL1RN*A2; genotype AA of the TNF-α*-308G>A polymorphic site; haplotypes TNF-α*-308A-LTA*252A and IL1B*-511C-IL1B*3953T-IL1RN*A2, on the contrary, are associated with a reduced risk of developing congenital pneumonia in RDS newborns.

According to P. S. Patwari et al. [151], in children with community-acquired pneumonia, the absence of the *A1 allele of the IL1RA gene was associated with an increased risk of a more severe course, the need for mechanical ventilation, and the development of acute lung injury or acute RDS. At the same time, in the Korean population there was no association of the polymorphic site IL-1β *-511C>T with the development of bronchopulmonary dysplasia.

The results of the study by Dawid S et al. [122] showed a higher prevalence of bronchopulmonary dysplasia of the following genotypes: IL-1RN; 86bp VNTR; GC and CC IL6 -174G>C; GA and AA IL6 -596 G>A; GA TNF-α-308G>A .Nevertheless, that data was not statistically significant. The authors concluded that further research is needed to determine which polymorphisms increase the risk of or protect against bronchopulmonary dysplasia.

Statistical analysis by a number of authors [38,83,133] showed the absence of an association of different genotypes of the C-590T polymorphism of the IL-4 gene in sick children with obstructive bronchitis, both acute and recurrent. An analysis of the C-590T polymorphism of the IL-4 gene revealed an association of the T/T genotype with the development of asthma in children. Also, research conducted by Yarilin A.A. [113] demonstrated that among a

large number of genes, interleukin 4 genes are involved in the formation of recurrent bronchitis in children.

Research conducted by Ji-Hong Zhang. et al. [135] demonstrated a greater likelihood of asthma in children with the homozygous T/T genotype than in children with the CC genotype (OR = 8.91, 95% CI = 1.89, 41.98). And the likelihood of asthma in children with the T allele was significantly higher and was 3.07 times greater than in children with the C allele (OR = 3.07, 95% CI = 1.50, 6.27).

F.F. Rizvanova [70] noted that CG polymorphisms of the IL6 gene (-174) and CT polymorphisms of the IL4 gene (-590) are associated with the risk of developing acute pulmonary diseases in children, differentiates on age and gender. Polymorphisms of the TNF-α (-308) G/A gene and the IL-1β (+3953) T/C gene are protective factors against acute bronchitis and community-acquired pneumonia in children.

In summary, it should be noted that today it is quite obvious that special attention is paid to cytokine regulation genes in the development of diseases, including the respiratory system.

In spite of that the problem of pathology of the respiratory system in children is sufficiently covered in the literature and an effective program for its treatment and prevention has been developed, identifying the genetic basis of bronchopulmonary diseases remains poorly understood [118

After reviewing the literature, we found that children with lymphatic diathesis have a predisposition to recurrent diseases of the bronchopulmonary system, tuberculosis, cancer and autoimmune diseases. However, we did not find data indicating the role of polymorphism of pro- and anti-inflammatory cytokine genes in the development of recurrent bronchitis in children with lymphatic diathesis.

Identification of genetic markers of predisposition to the development of recurrent bronchitis in patients with lymphatic-hypoplastic diathesis will make it possible to identify risk groups, which will open up opportunities for the use of prevention algorithms, as well as for standardized treatment of these patients.

1.3 Structure and features of morbidity in children with lymphatic-hypoplastic diathesis

Lymphatic-hypoplastic diathesis, as a constitutional anomaly, was first introduced in 1889-1890 by the Viennese pediatrician T. Escherich and pathologist R. Paltauf.

The prevalence of LHD is lower than that of exudative-catarrhal disease and is 10-12% [7,14].

In recent decades, there has been a steady increase in lymphatic diathesis, reaching 27.8±2.6% among the child population [53].

The maximum frequency of LGD is observed in preschool age, amounting to M.S. Maslov (1926) 3.2-6.8%, Yu.E. Veltishchev (1985) 11% and according to S.Yu. Makarov (2015) 12.5-24% of children.

Lastovka I.N. [45] believes that signs of LGD can be detected in 10-13% of young children. According to Vozgoment O.V. [16], LGD is formed by 2-3 years of life and, as a rule, ends by puberty.

Kuzmenko L.G. [111,140] indicates that in children with LGD at the age of 3-5 years, manifestations of lymphadenopathy quite often disappear, the size of the thymus is normalized, respiratory morbidity is reduced to the population level, and the “immune profile” of the blood is restored. In her opinion, the thymus seems to “mature” qualitatively, later in time it reaches a “plateau” of optimal functioning, and then undergoes age-related involution.

With LGD according to A.P. Moschich [50,53], thymomegaly is detected in approximately 70% of cases.

According to P.D. Vaganova et al. (14), among children with acute and protracted diseases of the bronchopulmonary apparatus, the detection of thymomegaly, as the main pathogenetic marker of LHD, is 30-32%.

A number of researchers have found thymomegaly in 10-50% of children. Most often this condition is registered in children of the first year of life: 40% in boys and 30% in girls [20,21,48,112]. According to Yu.I. Rovda [71]; thymomegaly occurs in 12.8% of young children; according to Yu.P. Tkachenko in 29.9% [26]; D.A Mudrak 37.1% [54].

Veltishchev Yu.E. [71] and in the work of M.Yu. Fedorova showed that lymphatic diathesis and its pathogenetic varieties are characterized by a polygenic type of inheritance with a predominant susceptibility to males. Having a polygenic basis, pathogenetic markers for LHD are lymphocytosis and a decrease in glucocorticoid activity of the adrenal cortex [110, 144].

It is known that the state of the immune system plays an important role in the pathogenesis of acute inflammation, its relapses and chronicity [91].

From the literature it is known that immunodeficiency, which is accompanied by pathology of the respiratory system, in certain cases is associated with an enlargement of the thymus [7,14,28].

The thymus is the central organ of immuno- and lymphocytopoiesis [14,121, 139,162].

As is known, the synthesis of biologically active substances occurs in the thymus, which are both secreted into the blood and act locally [140]. In addition, thymosin peptides induce the maturation of T lymphocytes, increase their mitotic activity, and increase the reactivity of T helper cells [14,29,71,72].

The available data in the literature regarding the immune aspect accompanied by lymphatic diathesis and thymomegaly is heterogeneous. Many authors point to the hypofunction of the T-cell component of the immune system: a decrease in the number of T-lymphocytes and a change in their subpopulation composition [14,175]. Studying T cell immunity in children with thymomegaly Vaganov P.D. et al. [14] define T-lymphopenia affecting both CD4 and CD8 cells, and these changes increased in parallel with the increase in the degree of thymomegaly.

A number of researchers paid attention to thymomegaly as a prognostic marker for the course of infectious processes in young children [44,45,61,165]. Other authors have found that in somatic pathology associated with lymphatic diathesis, an increase in the level of CD8+ and IgM is observed [127]. At the same time, other studies found the opposite results [46].

Research results by A.I. Smiyan et al[89] in young children with acute obstructive bronchitis against the background of thymomegaly, a more significant decrease in the content of lymphocytes, CD3+, CD4+, CD8+ and an increase in subpopulations of B-lymphocytes, as well as a decrease in the concentration of IgM, IgA and an increase in the level of IgG were revealed compared to patients without thymomegaly. In acute pathology of the respiratory system in young children, an increase in the level of CD8, CD16 and CD20 was detected, while an insufficient decrease in the level of IgA, IgM, and IgG was established.

There are domestic and foreign literary data directly indicating a connection between high respiratory morbidity and the syndrome of an enlarged thymus gland and thymomegaly [22,48,85,127, 174].

M. G. Lukashevich and T. N. Surazakova [48] also noted a high incidence of morbidity in children with an enlarged thymus gland.

Kuzmenko L.G. et al. [140] established a relationship between high respiratory morbidity and LHD, which is accompanied by a low level of lymphocytes with the CD3, CD4, CD8 phenotype.

According to Rovda Yu.I. et al [71,72] one of the main signs of LHD is a high incidence of acute respiratory viral infections, bronchitis, tracheitis, otitis, conjunctivitis, blepharitis, mainly of viral origin.

A number of researchers [44, 45, 71] have found that in children with thymomegaly, acute respiratory infections are more severe than in children without thymomegaly, while this was most clearly observed in children with grade III thymomegaly. The authors connect the frequency of occurrence of molinic forms of meningococcal infection with the degree of enlargement of the thymus: at stage I. 4.8% of the total, with II and III degrees. 85.2%, respectively.

Sorokman T.V. et al. [165], analyzing data on the relationship between the size of the thymus and respiratory morbidity, present the following statistics: thymomegaly is more common in obstructive types of damage to the respiratory tract, namely in stenosing laryngotracheitis and obstructive bronchitis; respectively, and in 23.5% up to the first stage. A different trend was observed in non-obstructive variants of bronchial lesions: the thymus was enlarged to stage I. in 62.5%, up to stage III. in 37.5% of patients [165].

Research by A.N. Bakhodirova et al. [11] showed that the severity of respiratory failure in children, in addition to the general toxic manifestation of a respiratory disease, is also influenced by the presence of a burdened premorbid background, in particular the presence of lymphatic-hypoplastic diathesis (12%).

According to the literature, a significant number of cases of sudden death syndrome are associated with thymic-lymphatic conditions, similar in etiopathogenesis to LHD [72,73].

When conducting a post-mortem examination of the medical records of children who died suddenly or unexpectedly from acute respiratory viral infections and pneumonia, pathological examination in most cases revealed signs of lymphatic-hypoplastic diathesis, which was accompanied by insufficiency of the lymphatic system and adrenal dysfunction [16,105]. A study conducted by Rovda Yu.I. et al. [72], also proves that in children with

LD the addition of pneumonia leads to the rapid development of signs of infectious toxicosis, respiratory and cardiovascular failure.

And also, in addition to the excessive level of respiratory morbidity in LGD and the high frequency of bacterial complications, a number of authors note a higher mortality rate in this category of children [105,139].

Studying the effect of constitutional anomalies on tuberculosis infection in children, Yu. A. Yarovaya et al. [114], showed the severity of intoxication syndrome in children with LHD than in children with NAD and AD. In addition, children with LGD had unfavorable forms, such as subacute disseminated tuberculosis and infiltrative pulmonary tuberculosis, which was not observed in groups of children with other types of diathesis

In children with LHD, intercurrent infections more often tend to be generalized, fulminant or recurrent with prolonged low-grade fever [44, 45].

E. Chkhartishvili [120] associates the presence of thymomegaly with recurrent episodes of various conditions, such as rash, dermatitis, upper and lower respiratory tract infections, sinusitis, chronic cough, hypertrophy of the adenoids and tonsils.

Pneumonia in patients with thymomegaly is characterized by a more protracted and severe course: with complicated forms and manifestations of degree II-III respiratory failure, neurotoxicosis and pulmonary edema [71, 72].

Equils O and Kelogg C [138] suggest that measuring thymic function by quantifying the T-receptor excision ring -TREC may help assess the risk of patients developing comorbid conditions, severe COVID-19 and other opportunistic infections, and may also predict patient's reaction to vaccination

It is possible that there are certain reasons for such a temporary delay in the development of the morphofunctional status of the IV, for example, fetal or genetic.

There are observations that among children and adults (in the past the so-called “lymphatics”), oncological diseases and diffuse connective tissue diseases are more likely to occur in the future [71,139,140], and they are more likely to develop tuberculosis.

It is known from the literature that any type of lymphatic diathesis is a risk factor for leukemia [139], autoimmune and neoplastic processes [140], and the development of secondary failure of the body’s adaptive and constitutional

defense systems, which causes a torpid, complicated course of infectious processes [100,156].

By reviewing the literature, we found that children with LGD have an immunodeficiency with a predisposition to diseases of the bronchopulmonary system, tuberculosis, oncological and autoimmune diseases. However, the literature data extremely poorly reflect the problem of the immune status of children with lymphatic diathesis, and the available data is contradictory and the literature practically does not describe the state of immunity and cytokine status in RB against the background of lymphatic diathesis in children, there is no data on the role of polymorphism of pro- and anti-inflammatory cytokine genes in the development RB in children with lymphatic-hypoplastic diathesis

Summarizing the above data, it seems relevant to study the immune status in patients with RB against the background of lymphatic-hypoplastic diathesis.

Chapter II. CLINICAL CHARACTERISTICS OF CHILDREN, RESEARCH METHODS USED

2.1. General characteristics of clinical material

The work performed presents the results of a dynamic clinical-immunological, hormonal, molecular genetic study of 119 children with acute bronchitis aged 2 to 7 years. The medial age of the examined patients was 4.1±0.82 years. The work was carried out in the children's department of the multidisciplinary clinic of SamState Medical University and in the pulmonology department of the Medical Children's Hospital of Samarkand for the period 2019-2021. The diagnosis of RB was established on the basis of clinical and radiological criteria confirmed in ICD 10 (J40.0). The diagnosis of LHD was created in basis of clinical, laboratory and radiological studies. RB was verified on the basis of pathognomonic, clinical manifestations of the disease - complaints (low-grade fever, cough, diffuse dry and moist rales in the lungs), a thorough history of the child's life and illness (repeated episodes of acute bronchitis 2-3 times or more during the year against the background acute respiratory infection) and radiological data (changes in the pulmonary pattern in the absence of infiltrative and focal shadows in the lungs).

All patients were divided into 2 groups: Group I included 62 (52%) patients with recurrent bronchitis, of which 35 (56%) were boys and 27 (34%) were girls. Group II included 57 (48%) patients with recurrent bronchitis due to LHD: 42 (74%) boys and 15 (26%) girls (Table 2.1). The control group consisted of 110 conditionally healthy children of the same age.

Table 2.1

Distribution of patients depending on the clinical variant and age of the patient

		Age of patients, years			
		2-3 года	4-5 лет	6-7 лет	Всего
Recurrent bronchitis	with bronchial obstruction	5(38,46%)	9(34,61%)	6(25%)	20(32,25%)
	without bronchial obstruction	7(61,54%)	17(65,39%	18(75%)	42(67,75%)

Recurrent bronchitis due to lymphatic-hypoplastic diathesis	with bronchial obstruction	32(71,1%)	9(20%)	4(8,89%)	45(78,9%)
	without bronchial obstruction	2(16,67%)	4(33,3%)	6(50%)	12(21%)

In patients of the second group, during the initial examination, attention was paid to the external signs of LHD, the condition of the thymus and peripheral lymphoid organs. In 48 (84.2%) patients, pastous habitus was noted, which was usually noted from birth. In 35 (61.4%) patients, birth weight was high, with excessive weight and length gain during the first year of life. All patients alongside RB on the background of LHD, thymomegaly was detected in 45 (79%) patients. The degree of thymomegaly was determined by assessing the size of the thymus gland on a chest radiograph based on the value of the cardio-thymic-thoracic index: the ratio of the width of the thymus to the width of the chest at the level of the domes of the diaphragm.

Thymomegaly I degree (CTTI 0.33-0.36) was detected in 10 (22.3%) patients, II (CTTI 0.37-0.42) in 18 (40%) and III degree (CTTI 0, 43 and more) - in 17 (37.7%) sick children. At the same time, an increase in the right lobe of the gland was observed in 12 (26.66%), the left lobe in 19 (42.22%), and in 14 (31.11%) patients, bilateral enlargement of the thymus gland was observed.

All sick children included in the study were examined in hospital and after discharge, according to a unified examination program created in accordance with the objectives of this study.

2.2. Clinical characteristics of the studied patients

Data on the distribution of clinical variants and depending on broncho-obstructive syndrome in patients are presented in Table 2.1.

As can be seen from table 2.1. in 20 (32.25%) patients of group I, exacerbations of the disease occurred with broncho-obstructive syndrome, while in patients of group II, broncho-obstructive syndrome was observed in 45 (78.9%) children. Broncho-obstructive syndrome in patients of group I was more often detected before 5 years of age, whereas in patients of group II, broncho-obstruction was detected in all age groups.

Based on the results of anamnestic data, attention was drawn to the high somatic morbidity in mothers of group II patients. At the same time, mothers of group II often had such pathology as chronic tonsillitis - in 26(45.6%), in 14(24.6%) mothers - hypertension, in 12(21%) pyelonephritis, in 27(47. 4%) of mothers experienced gestosis during pregnancy and in 39 (68.4%) the pregnancy proceeded with anemia of II, III degrees. In six families (10.5%) with two children, RB on the background of LGD was diagnosed in both children. Analyzing perinatal and antenatal factors, which were, the most significant predictors in the development of RB in children of group I were anemia in 77.4% of cases, a burdened history of chronic bronchitis in 23 (37.1%) and allergic diseases in 19 (30.64%). %) table 2.1.

Table 2.2.

Extragenital pathology of mothers

Groups / Pathology	Recurrent bronchitis		Recurrent bronchitis due to LHD	
	абс.	%	абс.	%
ARI in the early stages pregnancy	19	30,64	22	38,6
Chronic tonsillitis	10	16,12	26	45,6
MBC diseases (cystitis, pyelectasia)	1	1,6	8	14
Chronic pyeloniphritis	8	12,9	12	21
Hypertonic disease	7	11,29	12	21
Gastrointestinal pathology (chronic gastritis, cholecystitis)	12	19,35	14	24,6
Anemia	48	77,4	51	89,47
Chronical bronchitis	23	37,1	8	14,03
Allergic disease	19	30,64	10	17,5
Preeclampsia	13	22,6	27	47,36

When studying the frequency of relapses of the disease, we found that in patients of group II with grade I thymomegaly, relapses of bronchitis were repeated 4-5 times a year, in patients with grade II thymomegaly 5-6 times and in grade III thymomegaly relapses were repeated 6-8 times a year, while in In group I patients, the frequency of relapses was observed 3-4 times a year.

The distribution of those examined by gender showed (Fig. 2.1) a predominance of boys both in group I of patients with recurrent bronchitis (boys - 35 (56%), girls - 27 (34%), and in group II of patients - recurrent bronchitis against the background of LGD (boys - 42 (74%), girls - 15 (26%), which corresponds to literature data [5].

The general condition of patients upon admission to the hospital is indicated in Table 2.3.

Table 2.3.

General condition of patients with recurrent bronchitis upon admission

Condition of the patients	Group I	Group II
Heavy	9(14,5%)	15(26,32%)
Moderate	17(27,41%)	19 (33,33%)
Lung	36(58,1%)	23(40,35%)

As can be seen from table 2.3. in patients with lymphatic diathesis, 15 (26.32%) patients had a severe exacerbation of the disease, while in patients of group I, only 9 (14.5%) had a severe condition upon admission.

Research methods

The molecular genetic part of the work was carried out on the basis of the Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan, in the Department of Molecular Medicine and Cell Technologies (head, Professor Karimov Kh.Ya.).

Polymorphisms of TNF-α G308A of the rs 1800629 gene, IL-6 C174G of the rs1143627 gene, IL-β rs1143627 and IL-10 C592A of the rs1800872 gene, IL-4 C589T of the rs 2243250 gene were studied by PCR using the SPN Express test systems of SPF Litech "and Synthol, Moscow.

Genotyping of these markers consisted of several stages:

1. Sampling of peripheral blood.

2. Isolation of DNA molecules from lymphocytes.

3. Detection of polymorphisms by PCR;

4. Separation of PCR products by electrophoresis and visualization of the results obtained.

A comparative analysis of polymorphisms rs 1800629, rs1143627, rs1143627, rs1800872, rs 2243250 gene was carried out using a case-control model (comparisons of two comparative samples). The case sample consisted of 119 patients. The standard age of these patients was 4.1±0.82. Under control sample comprised of 110 conditionally healthy donors of Uzbek nationality, without any pathologies. The control group did not differ from the patient group in both gender and age.

The biomaterial was collected using standard vacuum tubes containing the anticoagulant EDTA-K3 (Vacutainer Becton Dickinson International, USA). Genomic DNA for PCR studies was isolated using the Amply Prime RIBO-prep reagent kit (Next Bio, Russia). The concentration of genomic DNA was measured using a Nano Drop 2000 spectrophotometer (Nano Drop echnologies, USA) at a wavelength of A260/280 nm. The purity of all DNA samples was 1.7/1.8. Detection of genetic loci TNF-α G308A gene rs 1800629, IL-6 C174G gene rs1143627, IL-β rs1143627 and IL-10 C592A gene rs1800872, IL-4 C589T gene rs 2243250 was carried out by allele-specific PCR followed by electrophoretic separation of products amplification.

PCR analysis was carried out using thermal cyclers CG1-96 (Corbett Research QUAGEN Germany) and Applied Biosystems (model 2720, USA) and in accordance with the following amplification programs

preliminary denaturation – 940C (10 min. 1 cycle), 13000 amplification cycles: 940C (30 sec) – denaturation, 65C (30 sec) – primer annealing, 650C (30 sec) – elongation, and final synthesis 720C (1 min 1 -cycle), 10 min storage.

Separation of amplified fragment products. those. PCR results were recorded in a 2% agarose gel prepared in a special TAE buffer using horizontal electrophoresis. For visualization of PCR fragments. i.e., the results of electrophoresis used a 1% solution of ethyl bromide dye. Fragments of the analyzed PCR products (DNA) were visualized on a UV-trans illuminator (with a wavelength of 310 nm) with a built-in digital camera. The results of the analysis of the fluorescent signal for each of the samples make it possible to give an answer about the presence or absence of each allele in hetero- or homozygous form.

In accordance with the manufacturer's instructions, polymorphic "mutant" and normal (wild) alleles of TNF-α G308A gene rs 1800629, IL-6 C174G gene rs1143627, IL-β T31C rs1143627 and IL-10 C592A gene rs1800872, IL-4 C589T gene rs 2243250 were determined based on the intensity and combination of bands of amplified fragments in "normal" and "pathological", interpreted as wild normal homozygous, heterozygous and unfavorable homozygous genotypes. Results of testing and determining the frequency of genotypes and alleles of the locus rs 1800629 TNF-α G308A gene, rs1143627 IL-6 C174G gene, rs1143627 IL-β T31C and rs1800872 IL-10 C592A gene, rs 2243250 IL-4 C589T gene in subgroups I and II patients and the control group are presented in Fig. 1,2, 3 and tables 1 and 2.

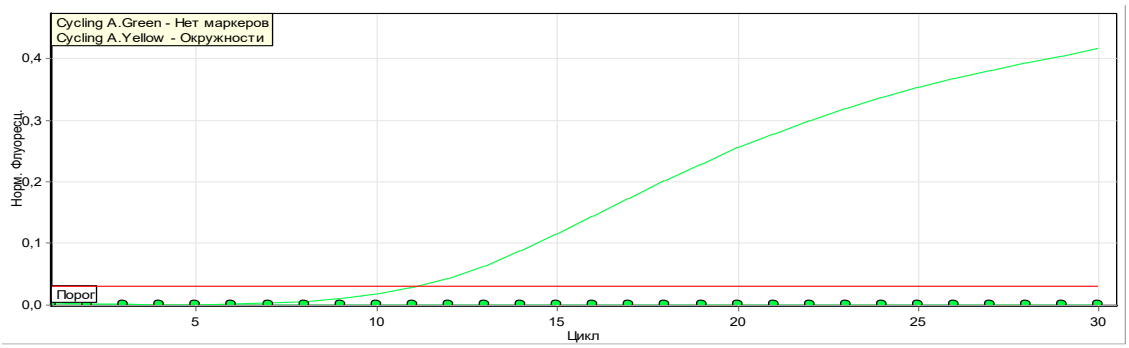


Fig.1. The result of real-time PCR for the TNF-α G308A gene, IL-6 C174G gene, IL-β T31C and IL-10 C592A gene, IL-4 C589T (detection of wild type gene - normal

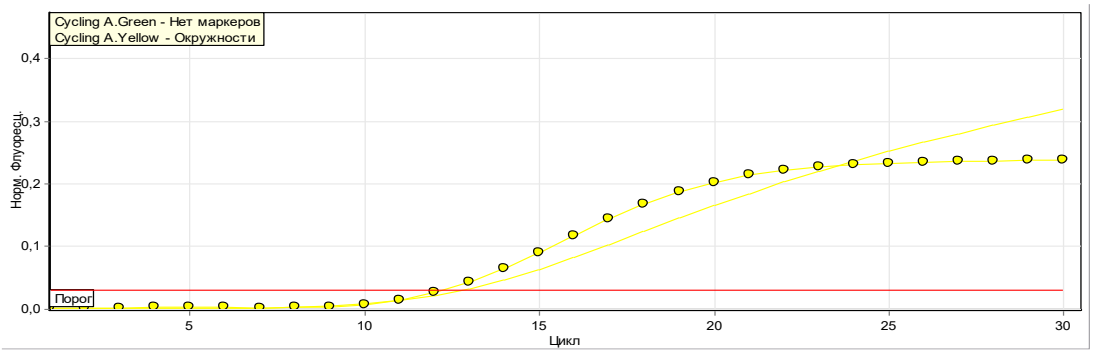


Fig.2. The result of real-time PCR for a gene. TNF-α G308A gene, IL-6 C174G gene, IL-β T31C and IL-10 C592A gene, IL-4 C589T (detection of heterozygous form of the gene

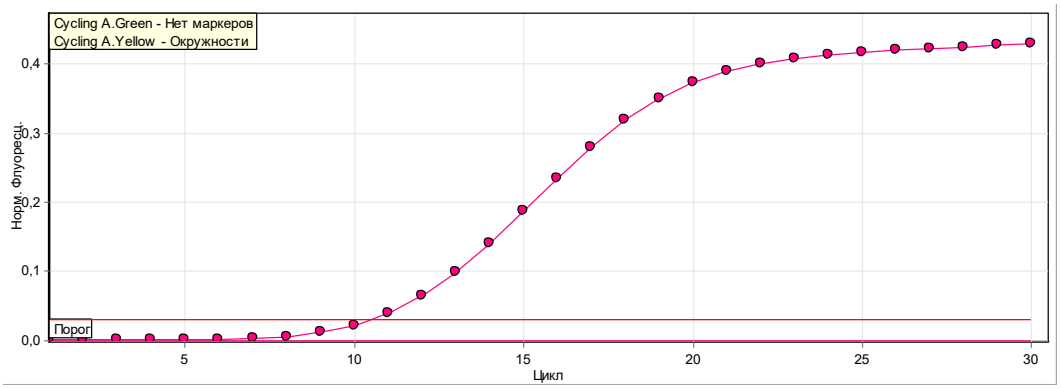


Fig.3. The result of real-time PCR for the TNF-α G308A gene, IL-6 C174G gene, IL-β T31C and IL-10 C592A gene, IL-4 C589T (detection of the mutant form of the gene

Immunological studies

Isolation of lymphocytes according to Boum (1974) on a ficcola verografin gradient with a density of 1.077 g/cm. The number of circulating T-lymphocytes was assessed by the method of spontaneous rosette formation according to Jondal et.al., (1972). Determination of T-lymphocytes, T-suppressors, T-helpers and B-rosette-forming lymphocytes (in reaction with mouse erythrocytes) was carried out according to I.V. Ponyakina and K.A. Lebedev (1983). Quantitative determination of the concentration of immunoglobulins of the main classes IgG, IgA, IgM, IgE was carried out using a set of reagents for highly sensitive enzyme immunoassay determination of immunoglobulins in blood serum of Vector Best LLC (Novosibirsk, Russia), by the enzyme-linked immunosorbent assay method, which is based on a two-stage “sandwich” version of the enzyme-linked immunosorbent assay using monoclonal antibodies to IgG, IgA, IgM, IgE according to the attached instructions. The study was conducted at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. Laboratory of immunology of reproduction.

Determination of cytokine levels

The level of cytokines IL-1β, TNFα IL-6, IL-4, IL-10 in blood serum was determined by sandwich enzyme-linked immunosorbent assay methods using test systems from Vector-Best.

Blood sampling for all children was performed in the morning (at 7-8 o'clock) from the cubital vein. Blood serum was obtained by centrifugation at 1500 rpm for 5 minutes in the same mode to remove platelet aggregates. The

mixture was mechanically stirred for 10 minutes and the resulting serum samples were stored at minus 250 C. The studies were carried out at the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.

Hormone research. To clarify the role of the pituitary-adrenal cortex in the regulation of the immune response, the basal level of adrenocorticotropic hormone (ACTH), somatotropic hormone (GH) and cortisol in the blood serum was determined by enzyme-linked immunosorbent assay using standard kits from Human (Germany).

The research material was the blood serum of patients, stored until the time of research in a freezer at a temperature of -20°C.

Mathematical methods of analysis

Assessment of the deviation of the distributions of genotypes of polymorphisms TNFα G308A gene IL-6 C174G gene, IL-β and IL-10 C592A gene, IL-4 C589T gene from the canonical distribution according to Hardy-Weinberg (HW) was carried out using a computer program for analyzing genetic data "Gene" Pop" ("Genetics of Population"), available on the Internet (http://wbiomed.curtin.edu.au/genepop).

Calculations of allele frequencies of TNFα G308A gene IL-6 C174G gene, IL-β and IL-10 C592A gene, IL-4 C589T were carried p=(2np+npq)/2N, where N is the sample size; np – number of homozygotes for the p allele; npq – number of heterozygotes. Actual (observed) heterozygosity: Hobs=N0/N, where N0 is the number of heterozygotes. Theoretical (expected) heterozygosity: Hexp=1 – Σpi2, where pi is the frequency of the i allele. i=1out using the following formula

p=(2np+npq)/2N, where N is the sample size;

np – number of homozygotes for the p allele;

npq – number of heterozygotes. Actual (observed) heterozygosity: Hobs=N0/N, where N0 is the number of heterozygotes.

Theoretical (expected) heterozygosity:

Hexp=1 – Σpi2, where pi is the frequency of the i allele.

i=1

The coefficient of deviation of actual heterozygosity from the theoretical one was calculated using the following formula: F= (Hexp –Hobs)/Hexp.

In order to assess the prognostic effectiveness of each genetic marker TNFα G308A gene, IL-6 C174G gene, IL-β and IL-10 C592A gene, IL-4 C589T sensitivity (SE), specificity (SP) and AUC (area under curve) were calculated. The prognostic efficiency of polymorphic loci was determined as follows: if the AUC value is <0.5, then the genetic marker is random; 0.5<AUC>0.6 – poor marker, 0.6<AUC>0.7 – average; 0.7<AUC>0.8 – good; AUC>0.8 is an excellent classifier [http://vigg.ru/fileadmin/user_upload/Rubanovich/].

The degree of associations of allelic and genotypic variants was assessed in the values of OR and RR indicators with a 95% confidence interval (95% CI

The prognostic efficiency of polymorphic loci was determined as follows: if the AUC value is <0.5, then the genetic marker is random; 0.5<AUC>0.6 – poor marker, 0.6<AUC>0.7 – average; 0.7<AUC>0.8 – good; AUC>0.8 is an excellent classifier [http://vigg.ru/fileadmin/user_upload/Rubanovich/].

The application package “OpenEpi 2009, Version 2.3” was used as a tool for calculating the obtained data.

Chapter III. CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF SICK CHILDREN WITH RECURRENT BRONCHITIS

3.1. Comparative clinical characteristics of patients with recurrent bronchitis and recurrent bronchitis against the background of lymphatic-hypoplastic diathesis

There were 119 patients under our supervision. All patients were divided into 2 groups: Group I included 62 (52%) patients with recurrent bronchitis. Group II included 57 (48%) patients with recurrent bronchitis due to LHD.

All patients were hospitalized in the acute period of recurrent bronchitis

In patients of the second group, during the initial examination, we paid attention to the external signs of LGD, the condition of the thymus and peripheral lymphoid organs. In 48 (84.2%) patients, pastous habitus was noted, which was usually noted from birth. In 35 (61.4%) patients, birth weight was high and was accompanied by excessive weight and length gain during the first year of life. Thymomegaly in patients of group II was determined in 45 (79%) patients: degree I thymomegaly was detected in 6 (3.6%) patients, degree II in 22 (40.35%) and degree III in 17 (21.1%) patients children.

Upon admission to the hospital, 15 (26.32%) patients in group II had a severe general condition, while in patients in group I only 9 (14.5%) had it.

Seasonality of exacerbations was identified in 51 (82.3%) patients in group I. Exacerbations in this group were observed more often in the autumn-winter period, and somewhat less frequently in the spring. In patients of group II, we did not observe seasonality of exacerbation; relapses of the disease occurred throughout the year.

The main complaints during the exacerbation period (Table 3.1.) of patients in group I were: runny nose, cough, rise in temperature, malaise, loss of appetite. However, in the group of patients with RB against the background of LHD, the more frequent complaints were increased body temperature, cough, expiratory shortness of breath, distant wheezing, weakness, headache, sweating, decreased appetite and sleep disturbance.

Table 3.1.

Clinical manifestations of recurrent bronchitis in children of groups I and II

Complaints	Recurrent bronchitis Group I n=62	Recurrent bronchitis due to LHD Group II n=57	RR	95% confidence interval (RR)
Runny nose	53(85,5%)	3(5,3%)	16,2	(5,39- 48,84)
Cough	62(100%)	57(100%)	1,0	(1- 1)
Temperature rise	51(82,3%)	57(100%)	0,8	(0,73- 0,92)
Malaise	34(54,8%)	49(86,3%)	0,6	(0,49- 0,81)
Decreased appetite	62(100%)	57(100%)	1,0	(1- 1)
Dyspnea	22(35,5%)	42(73,7%)	0,5	(0,33- 0,69)
Remote wheezing	19(30,6%)	44(77,2%)	0,4	(0,26- 0,59)
Weakness	29(46,7%)	51(90%)	0,5	(0,4- 0,69)
Sleep disturbance	30(48,3%)	46(80,7%)	0,6	(0,45- 0,8)
Headache	28(45,2%)	41(72,%)	0,6	(0,46- 0,86)
Sweating	22(35%)	56(98%)	0,4	(0,25- 0,5)

The clinical picture of RB in patients of group I was typical. Moderately severe intoxication in the acute period of the disease was noted in 51 (82.3%) children. In 11 (17.7%) patients of group I, the exacerbation of the disease occurred without an increase in temperature, and in 51 (82.3%) we observed an increase in temperature to subfebrile levels at the beginning of the exacerbation. Whereas, all patients in group II experienced an increase in body temperature (to high temperatures in 21% of children and low-grade fever in 79% of children) at the onset of the disease. Dyspnea was detected in all patients of group II and lasted 3.6±1.4 days, in patients of group I in 26.6% and lasted 2.3±0.6 days $P<0.05$.

The increase in temperature was accompanied by the appearance of a cough. In patients of the first group, a dry cough was mainly observed, and in 16 (25.8%) patients, from 2-4 days, it transformed into a wet cough. While 45 (78.9%) patients in group II had a wet cough.

Thus, children of group I more often had a long-lasting (18.8±4.2) dry cough compared to patients of group II, in whom a wet cough predominated.

In 22 (35%) children of the first group, bronchitis occurred with obstructive syndrome and in 40 (65%) children - as simple bronchitis without obstruction. Whereas in patients of the second group of 57 children, 52 (91.2%) exacerbation of RB occurred with obstructive syndrome and only 5 (8.8%) children - in the form of simple bronchitis (without obstruction). It was characteristic that bronchial obstruction in patients of group I was more often observed at the age of 2-3 years, while in patients of group II obstructive syndrome was observed in all age groups.

In 53 (85.5%) patients of group I, the percussion sound over the lungs remained pulmonary and in 9 (14.5%) patients the percussion sound changed to a boxy tone. Whereas in patients of group II, 35 (61.4%) had a box tone and in 22 (38.6%) the percussion sound over the lungs remained pulmonary. Auscultatory data in 25 (40.3%) patients of group I were dry rales against the background of hard breathing, and in 17 (27.4%) patients large and medium-bubbling wet rales were heard. In 35.5% of this group of patients with obstructive syndrome, prolonged and whistling exhalation was noted. Auscultation Comparison of chest X-ray data revealed some group differences. Thus, in children with RB without LHD, the X-ray picture was characterized mainly by expansion of the roots of the lungs, an increase in the pulmonary pattern mainly in the hilar zones. In the group of patients with RB that developed against the background of LHD, the most characteristic feature was a pronounced increase in the pulmonary pattern throughout the entire pulmonary field; in addition, there was an increase in the airiness of the pulmonary field on both sides. medium-bubble wet rales in 44 (77.2%) and in 11 (19.3%) children there were dry rales against the background of hard breathing. 74% of patients in the second group with obstructive syndrome had a prolonged and wheezing exhalation. On average, the duration of exacerbation in patients of group I was 21±0.06 days, in patients of group II 32±0.06 days.

Comparison of chest X-ray data revealed some group differences. Thus, in children with RB without LHD, the X-ray picture was characterized mainly by expansion of the roots of the lungs, an increase in the pulmonary pattern mainly

in the hilar zones. In the group of patients with RB that developed against the background of LHD, the most characteristic feature was a pronounced increase in the pulmonary pattern throughout the entire pulmonary field; in addition, there was an increase in the airiness of the pulmonary field on both sides.

The duration of clinical manifestations of recurrent bronchitis and RB against the background of LHD is presented in Fig. 3.1.

Thus, the intoxication syndrome in patients of group I was relieved in the early stages of hospital stay (2-3 days), while in patients of group II only on days 3-5 of treatment.

Duration of clinical manifestations in patients with recurrent bronchitis and in children with recurrent bronchitis against the background of LHD (days

Thus, the intoxication syndrome in patients of group I was relieved in the early stages of hospital stay (2-3 days), while in patients of group II only on days 3-5 of treatment.

An analysis of the frequency of exacerbations of RB on the background of LGD, carried out taking into account the degree of enlargement of the thymus gland, showed that with thymomegaly of I degree, exacerbations of RB in this group were 4-5 times a year, with II - 5-6 times and with III degree, relapses were repeated 6-8 times a year once a year. This may indirectly confirm the severity of immune changes depending on the degree of thymic hypertrophy in children. In group I of patients, the frequency of exacerbations of RB averaged 3-4 per year.

In general, comparing groups I and II of patients, we can conclude that the clinical course of recurrent bronchitis in children with LGD has its own characteristics. The duration and severity of the process are characteristic. In addition, children with thymomegaly II and III degrees had a severe intoxication syndrome, accompanied by hectic and prolonged fever, as well as severe bronchial obstruction.

The identified features of the clinical picture of RB against the background of LHD in children are the basis for the use of appropriate treatment tactics and the development of adequate preventive care both at the stages of treatment in a hospital and clinic.

3.2. Features of the immune status and production of cytokines TNF-α, IL-4, IL-1β, IL-6, IL-10 in children with recurrent bronchitis against the background of lymphatic diathesis

It is known that early detection of reduced immunological reserves in children is the most important problem of modern pediatrics, allowing for targeted primary prevention of many widespread diseases, including recurrent respiratory diseases in children [107].

By differential calculation of the percentage of leukocytes (monocytes, granulocytes, lymphocytes) one can judge the possible immunological changes occurring in the body in response to a pathogenic agent (Table 3.2.1.).

Indicators %	Age 2-3 years		Age 4-5 years		Age 6-7 years	
	RB	RB against the background of LGD	RB	RB against the background of LGD	RB	RB against the background of LGD
Leukocytes	7,8±0,71	8,28±0,10*	6,1±0,28	7,2±0,32*	5,7±0,23	6,3±0,72
Rod nuclear neutrophil	5,1±0,48	5,2±0,82	4,72±0,67	4,9±0,83	3,45±0,38	4,1±0,65
Nuclear neutrophil segment	27,2±2,34	28,5±2,54	30,7±2,8	34,4±1,7	50,7±1,9	52,5±3,7
Eosinophil	3,3±0,45	3,8±0,72	3,2±0,58	4,5±0,82*	3,2±1,10	4,8±0,48*
Monocytes	7,17±0,78	8,25±0,56*	6,8±1,82	8,7±0,65	5,77±0,89	7,95±0,20
Lymphocyte	52,3±3,5	56,2±5,2*	46,4±3,4	48,35±3,8*	44,7±2,8	46,82±4,62

Table 3.2.1

Leukoformula indicators in children in the compared groups

Note - *regarding patients with RB on the background of LHD

As can be seen from table 3.2.1. in case of RB against the background of LGD, there are some differences in the leucoformula from the indicators of group I. Thus, there is a significant increase in the absolute values of leukocytes at the age of 2-3 years and 4-5 years ($p<0.05$), eosinophils at the age of 4-5 years ($p<0.05$), lymphocytes at the age of 2-3 years and 4 -5 years ($p<0.05$) and monocytes at the age of 2-3 years ($p<0.05$) in the group of

children with RB against the background of LHD.

It should be noted that the increase in the total number of leukocytes in patients of group II was associated with lymphocytosis in children aged 2-3 years and 4-5 years, apparently associated with a decrease in the level of thymic factors in the blood serum in this category of patients

In group I patients, the content of monocytes was reduced compared to healthy children, which may be due to a violation of their formation in the bone marrow or a significant need for them in tissues during inflammation.

Immunological studies in patients of both groups were carried out during the acute period of the disease.

Table 3.2.2.

Comparative characteristics of indicators of cellular and humoral immunity in RB in the compared groups.

№	Indicators	Conditionally healthy children n = 39	Recurrent bronchitis I-group n = 62	Recurrent bronchitis due to LHD II-group n =57
1	CD3+	57,88±1,39	48,4±0,96**	40,5±1,18***
2	CD3+CD4+ %	37,8±0,84	33,75±1,28**	29,7±0,92***
3	CD3+CD8+ %	24,25±0,65	23,26±0,51	21,63±0,67***
4	CD4+/CD8,	1,56±0,06	1,45±0,04**	1,37±0,08*
5	CD16+, %	19,51±0,31	18,7±0,19*	24,8±0,64***
6	CD19+, %	20,75±0,41	27,25±1,75***	17,63±1,23**

Note: * - differences relative to the data from the healthy group are significant (* - $P<0.05$, ** - $P<0.01$, *** - $P<0.001$

As a result of immunological studies, a more pronounced suppression of the T-cell immunity in children of the Republic of Belarus against the background of LHD was established than in the group of children of the Republic of Belarus without LHD (40.5±1.18% and 48.4±0.96%, respectively) ($p< 0.001$). The average percentage of leukocytes and lymphocytes was statistically significantly higher as thymomegaly progressed than in LGD children without thymomegaly and in healthy children. The average values of T-lymphocytes and their regulatory subpopulations were lower in LHD

children with thymomegaly than in LHD children without thymomegaly, as well as in healthy children. It should be noted that a direct correlation has been identified between the degree of thymomegaly and the number of leukocytes, lymphocytes (r=+0.71; r=+0.64), as well as an inverse correlation between the degree of thymomegaly and the number of T-lymphocytes and their subpopulations (r =-0.78; r =-0.68; r =-0.61). table 3.2.3

Table 3.2.3.

Characteristics of correlations between immunity indicators and the degree of thymomegaly

Indicators	LGD without thymomegaly	LGD with thymomegaly	
		I degree	II-III degree
Leukocytes	+0,233	+0,269	+0,71
Lymphocytes	+0,222	+0,293	+0,64
CD3+, %.	-0,304	-0,419	-0,78
CD3+CD8+	-0,201	-0,365	-0,61
CD3+CD4+	-0,336	-0,48	-0,68
Ig A	-0,25	-0,352	- 0,69

The relative content of T-helper cells had a clear tendency to decrease in patients of both groups compared to healthy children ($p<0.001$). A significant decrease in CD4+ content was noted in children of group II (29.7±0.92%) in contrast to patients in group I (32.75±1.28%, $p<0.01$). The CD8+ content in the blood of patients in both groups was reduced compared to the values of children in the control group ($p<0.01$). At the same time, the greatest decrease in CD8+ was detected in patients of group II (20.63±0.51% versus 23.75±0.51% in children of group I, $p<0.001$). When comparing changes in the components of immunity with the degree of thymomegaly, we found a decrease in the relative number of all types of T-lymphocytes, as well as CD8+, as thymomegaly progresses. As is known [35], CD8+ is a subpopulation marker and is expressed in humans on mature T lymphocytes. A significant decrease in the CD8+ count in children of group II is probably associated with a decrease in mature T-lymphocytes.

The quantitative imbalance of CD4+ and CD8+ cells led to a change in the immunoregulatory index in patients of both groups, in whom the

immunoregulatory index was 1.45±0.04 μl and 1.37±0.08 μl compared to healthy children ($p < 0.05$) .

In patients of group II, in contrast to patients of group I, there was a significant decrease in the CD4+/CD8+ index ($p < 0.01$).

In general, all the data presented above give the idea that in patients with RB against the background of LHD, the immunoregulatory function of T-lymphocytes is more reduced compared to patients with RB

When analyzing the CD16+ content, we found a significant increase in this indicator in patients with RB against the background of LHD compared to controls ($p<0.01$); in patients with RB, the content of CD16+ did not differ statistically significantly from similar indicators in the healthy group.

Thus, the greatest decrease in the relative content of T-lymphocytes in patients of group II with lymphatic diathesis is associated with a weakened migration of T-cells from the thymus to the peripheral part of the immune system, i.e., in these children the processes of differentiation of T-lymphocytes are weakened.

Analyzing the B-cell component of immunity and the humoral component based on the content of immunoglobulins, we found a significant decrease in B-lymphocytes in patients of group II, while in patients of group I there was a tendency to increase B-lymphocytes.

To characterize the humoral component of immunity, an analysis of the content of immunoglobulins in the blood serum of the examined children was carried out (Table 3.2.3.).

Table 3.2.3.

Indicators of humoral immunity in the studied children with RB.

№	Indicators	Conditionally healthy children n = 39	Recurrent bronchitis Group I n = 62	Recurrent bronchitis due to LHD II group n =57
1	Ig A (pg/ml)	1,04±0,05	0,58±0,064***	0,37±0,048***
2	Ig M (pg/ml)	1,13±0,04	1,83±0,08***	0,95±0,05***
3	Ig G (pg/ml)	10,77±0,63	11,4±0,41	8,87±0,38*
4	Ig E (pg/ml)	30,6±2,3	42,6±2,4***	36,8±1,9*

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

In sick children in group I, an increase in IgM levels was found during the period of exacerbation of the disease compared to healthy children (P<0.05), which indicates the presence of an infectious agent. Whereas, the level of IgM was significantly low in patients of group II and amounted to 0.95±0.05 pg/ml, which apparently indicates the inability of B-lymphocytes to adequately respond to an infectious agent in children against the background of LHD associated with the immaturity of these cells, and as a result, the inability to produce immunoglobulins.

When comparing changes in the level of IgM with the degree of thymomegaly, we found a more pronounced decrease in grade III thymomegaly 0.82 ± 0.065 pg/ml, while in grade I they corresponded to the normative indicators of 1.11 ± 0.06 pg/ml, in grade II there was a downward trend compared to the group of healthy children (1.03±0.07 pg/ml versus 1.13±0.04 pg/ml).

When studying the concentration of IgA in the blood serum of patients in group I, there was a significant decrease in the content of IgA compared to the control group, which indicates a decrease in the body's humoral defense. But lower IgA content was found in group II patients. Thus, in patients of group II, the IgA level was 2.8 times lower than the normative data (P<0.001). Also, we found an inverse correlation (-0.69) between the level of Ig A and the degree of thymomegaly. If in children in group II with grade I thymomegaly the Ig A content was 0.54±0.084 pg/ml, then in children with grade II-III thymomegaly it was 0.35±0.06 pg/ml (P<0. 05).

The study of Ig G content in the studied groups of patients revealed that its change in children with RB was not significantly significant and only tended to increase.

In children in the RB group with LHD, there was a significant decrease in IgG levels, respectively 11.4±0.41 pg/ml and 8.87±0.38 pg/ml (p<0.05). A decrease in serum IgG levels in children of group II may be associated with both a disruption in the process of switching the synthesis of IgG isotypes and a disruption in the formation of memory B cells.

IgE levels were high in patients of both groups (p<0.05). At the same time, in patients of the second group with grade II-III thymomegaly, the level of IgE

was more elevated compared to healthy children, respectively 44.7±2.3 pg/ml and 30.6±2.3 pg/ml (p<0. 05).

Thus, it was revealed that in the children with RB we studied, the immune response to the infectious agent was insufficient and was characterized either by the development of an infectious syndrome of secondary immunodeficiency, or by an excessive-hyperergic one, in which case an allergic syndrome of secondary immunodeficiency develops. Our study showed a combination of these syndromes often in patients with RB against the background of LHD.

The above indicates that with RB in children, there is dysregulation of both the cellular and humoral components of the immune response as a whole, the mechanisms of which are obviously associated with the activation of pro- and anti-inflammatory cytokines and the immunoregulatory effect of cytokines on T-helper cells type 1 and 2, as indicated by other studies [36,94].

As is known [94], the key cytokines in the development and maintenance of airway inflammation are mediators such as IL-1β, TNF-α, IL-4, IL-6 and IL-10. Cytokines have a wide range of biological activities and promote intercellular interactions during the immune and inflammatory response, serving as mediators of the immune system, regulating the strength and duration of the immune response, determining the type and intensity of the inflammatory process [94,113]

The study of the characteristics of the production of cytokines TNF-α, IL-4, IL-1β, IL-6, IL-10 and the study of their mechanisms of action in recurrent bronchitis in children showed that in children with RB and RB against the background of LHD, the production of pro- and anti-inflammatory cytokine levels significantly increased compared to healthy children (p <0.001). The results of the cytokine profile study are presented in Table 3.2.4.

Table 3.2.4.

The content of cytokines in children with RB (M±m)

Indicators	Conditionally healthy children n = 39	Recurrent bronchitis n=62	p	Recurrent bronchitis due to LHD n=57	p
IL-1β pg/ml	5,46±0,79	23,27±3,14	<0.0001	46,54±4,27	<0.0001
IL-10 pg/ml	9,01±0,87	36,8±3,06	<0.0001	23,24±2,93	<0.0001

IL- 4 pg/ml	4,61±0,64	16,90±1,05	<0.0001	11,75±1,70	<0.0001
IL- 6 pg/ml	6,6±0,81	26,28±2,66	<0.0001	51,47±3,50	<0.0001
TNFα pg/ml	6,6±0,81	30,41±1,97	<0.0001	46,66±3,69	<0.0001

As can be seen from table 3.2.4. in patients with RB against the background of LHD, the rate of IL-1β production was significantly ($p < 0.01$) increased to 46.54 ± 4.27 pg/ml, which was 8.5 times higher compared to the norm. In patients of group I, this cytokine was 4.2 times higher compared to healthy children. When studying the production of IL-1β depending on the degree of thymomegaly, we found a higher level of IL-1β in children with thymomegaly II - III degrees compared to patients with thymomegaly I degree, amounting to 58.62±6.27 pg/ml and 38. 78±4.34 pg/ml, respectively ($p<0.001$). It is known that IL-1β is the first to be included in the body's defense response to pathogenic factors [167]. This cytokine plays a key role in the development and regulation of nonspecific defense and specific immunity, and also regulates inflammatory and immune processes, activates neutrophils, T and B lymphocytes [167,168].

Our work shows that in children with RB, increased production of IL-1β leads to an increase in the proliferative response and endogenous activation of T cells. In patients of group II, the level of proliferative response to mitogen weakens with a weakening of the release of mature T cells from the thymus, which apparently leads to T lymphopenia. In patients with stage II-III thymomegaly, the deficiency of the T-cell component of the immune system was aggravated, and this contributed to the manifestation of its failure. By studying the correlation relationship, we established an inverse correlation between IL-1β and the number of T lymphocytes and their subpopulations ($r = -0.72$; $r = -0.66$; $r = -0.71$).

When assessing the production of IL-10, we found that in patients with RB against the background of LHD there was a tendency to decrease compared to patients with RB, respectively 23.24±2.93 pg/ml and 36.8±3.06 pg/ml ($p<0.001$). We know that IL-10 is an antagonist of IL-1β and is an anti-inflammatory cytokine. It is the ratio of the levels of these cytokines that most fully reflects the direction of the immune response and the activity of inflammation [167]. Our data show that in patients of group II the inflammation process is more severe.

There is a natural increase in the anti-inflammatory cytokine IL-4 in all examined groups, but it is more pronounced in patients of group I, exceeding the norm by 4 times. Apparently, this can be explained by the fact that in patients of group I, the proliferation and differentiation of B cells and antibody genesis are more preserved compared to group II.

When assessing the level of IL – 6 in patients of group II, a significant increase in IL-6 was found compared to a group of apparently healthy children, as well as with patients of group I: 51.47±3.50 pg/ml; 6.6±0.81 pg/ml and 26.28±2.66, respectively ($p<0.001$), which makes it possible to conclude a more severe clinical course of acute obstructive bronchitis against the background of LHD.

In our studies, the values of tumor necrosis factor-α in children with RB against the background of LHD were 7 times higher compared to the control group ($P<0.001$), while in patients of group I, this indicator increased 4.6 times. This reflects a more pronounced activity of macrophages involved in maintaining the inflammatory process in RB in children with LHD.

In general, the data obtained on the study of the role of pro- and anti-inflammatory cytokines allow us to conclude that the response to an infectious agent in children with RB, although it occurs against the background of immunodeficiency, is more adequate, whereas in children with RB with LHD, having reduced rates immune status, there is an imbalance in the immune response, which leads to a decrease in their overall resistance to the pathogen.

3.3. The state of somatotropic function of the pituitary gland and adrenal cortex in patients with recurrent bronchitis against the background of lymphatic-hypoplastic diathesis

It is known that the thymus gland is a “switchboard” in the interaction between the neuroendocrine and immune systems [14,56]. In this regard, there was a need to study the basal levels of ACTH, STH and cortisol in children with RB and RB against the background of LHD (Table 3.3.1).

As is known, the pituitary-adrenal system plays a role in maintaining the immune status of children [56,71]. At the same time, the central place in this system is given to growth hormone, which also has a thymotropic effect.

In order to assess the functional state of the pituitary-adrenal cortex system in children with RB and RB against the background of LHD, we examined 119 sick children aged 2 to 7 years. The first group consisted of 62 patients with RB and the second group of 57 patients with RB against the background of

LHD. The control group consisted of 39 practically healthy children of the same age.

results of studies of hormone content are presented in table. 3.3.1 Table 3.3.1 Basal level of ACTH, STH, cortisol in patients without exacerbation of the disease (M±m)

Indicators	Conditionally healthy children n=39	Recurrent bronchitis n=62	Recurrent bronchitis due to LHD n=57
STH ng/ml	1,83±0,21	2,95 ± 0,41**	2,02±0,19
ACTH pmol/l	12,2±2,31	12,9±2,21	6,7±2,31*
Cortisol ng/ml	210±15,91	185±14,82	215±16,71

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

As can be seen from table 3.3.1. the basal GH level in healthy children aged 2-7 years was 1.83±0.21 ng/ml, ACTH 12.2±2.31 pmol/l and cortisol level was 210±15.91 ng/ml.

When studying the relationship in healthy children, the level of growth hormone correlates to a moderate degree with T-helpers, IgM and IgG negatively, and B-lymphocytes and T-suppressors with a positive relationship. There is a negative relationship between cortisol and growth hormone (Table 3.3.2).

Table 3.3.2.

Correlation relationships between GH, ACTH and cortisol between immunological parameters in healthy children 2-7 years old.

Indicators	STG	ACTH	cortisol
CD3+	+0,014	+0,15	-0,347
CD4+	-0,44	+0,054	+0,373
CD8+	+0,19	+0,098	-0,247
CD19+	+0,24	+0,18	-0,21
IgA	-0,03	-0,48	+0,3
IgM	-0,4	-0,57	+0,087

IgG	-0,31	-0,23	+0,67
ACTH			-0,59
STG			-0, 47

Pituitary ACTH correlates with low B-lymphocyte levels (+0.18) and has an inverse relationship with cortisol and three classes of immunoglobulins. Positive correlative connections have been established between cortisol and two classes of Ig A and M in healthy children.

In general, the maintenance of a certain level of T-lymphocytes is facilitated by the physiological concentration of cortisol, and to a lesser extent by ACTH; T-helpers are inversely related to the level of growth hormone; and T-suppressors - from the level of cortisol. The level of immunoglobulins is directly dependent on the concentration of cortisol and inversely dependent on ACTH and STH. Under physiological conditions, there are negative relationships between cortisol and ACTH, as well as cortisol and GH, which help maintain the integrated interaction of the endocrine and immune systems in children.

The results of studies of hormone levels in the patients we studied showed that during the period of remission there was a slight increase in the concentration of cortisol and growth hormone and an almost twofold decrease in ACTH in children of the second group. The ACTH/cortisol ratio decreased by almost half and amounted to 0.031 versus 0.058 in healthy patients (Table 3.3.1).

In patients of group II during the period of exacerbation of the disease, a higher level of growth hormone (5.13±0.79 ng/ml) and a low value of ACTH (5.33±1.37 pmol/l) were revealed with an unreliable decrease in the level of cortisol (170.9± 10.36 nmol/l). A comparative assessment of the content of cortisol, ACTH and GH depending on the degree of enlargement of the thymus gland revealed that in children with thymomegaly II-III there was an increase in cortisol levels to 316±24.6 nmol/l, a more significant decrease in ACTH (5.12±1. 21 pmol/l) and a GH level 2 times higher than the normative data (4.02±0.4 ng/ml). The ACTH/cortisol ratio was only 0.016, which is 2.4 times lower than the physiological figure 3.3.1; 3.3.2.

As is known, steroid hormones weaken the production of thymulin, inhibit the synthesis of specific antibodies and inhibit the migration of lymphocytes from the intravenous fluid [71]. This fact was confirmed in our study, i.e. in

patients with RB with stage II-III thymomegaly, an increased level of cortisol during an exacerbation of the disease led to an increase in immunodeficiency. Table 3.3.3 Basal levels of ACTH, STH, cortisol in patients with exacerbations of the disease (M±m)

Indicators	Conditionally healthy children n=39	Recurrent bronchitis n=62	Recurrent bronchitis due to LHD n=57
STH ng/ml	1,83±0,21	1,21 ± 0,41	5,13±0,79 ***
ACTH pmol/l	12,2±2,31	20,2±4,9	5,33±1,37 **
Cortisol ng/ml	210±15,91	367±15,28***	170,9±10.36

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

Data analyzes show that in children of group II, cooperative connections in the ACTH/cortisol, ACTH/GH, and GH/cortisol systems are disrupted, as evidenced by not an inverse, but a direct correlation between their levels, as well as a weakening or disappearance of the correlation between them (Table 1). 3.3.4. Table 3.3.4 Correlation relationships of cortisol between ACTH, GH and immunological parameters.

Indicators	Healthy children	Group I	Group II
CD3+	-0,347	-0,275	-0,37
CD4+	+0,373	-0,26	-0,13
CD8+	-0,247	-0,43	-0,21
IgA	+0,3	-0,32	-0,16
IgM	+0,087	+0,37	+0,05
IgG	+0,67	+0,17	-0,11
АКТГ	-0,59	+0,57	+0,35
СТГ	-0, 47	-0,28	+0,019

Thus, the identified correlations in children indicate the presence of tension in the pituitary-adrenal system in children of group II and changes the correlation relationship with immunity indicators.

In patients of group I, it was found that the level of ACTH (20.2±4.9 pmol/l, $p < 0.05$) and cortisol in the blood plasma (367±15.28 ng/ml $p < 0.01$) during the exacerbation period RB significantly increased compared to healthy children, with subsequent normalization of ACTH during the period of remission of the disease, despite the absence of changes in cortisol levels. It should be noted that in the group of children who received systemic glucocorticosteroids immediately before admission to the hospital, a sharp decrease in cortisol levels was found (85.4±28.7ng/ml, $p<0.001$), probably associated with the depletion of the functional capacity of the adrenal cortex due to its suppression functions by the entry of exogenous hormone into the body. In non-exacerbation of the disease, a tendency towards normalization of cortisol levels was noted, but it did not reach the values obtained in the control group of practically healthy children.

Thus, the results of our studies give reason to believe that during the period of exacerbation of the disease, considered as stress of the body in response to a pathogen, the level of ACTH compensatory increases, which in turn stimulates the production of cortisol, but the feedback principle does not work sufficiently in the patients we studied . During the period of remission of RB, due to an increase in the affinity of the transcortin protein for cortisol, the level of free hormone decreases, and although the level of total cortisol remains elevated, the feedback mechanism begins to be fully realized.

Analysis of data from a study on the level of GH in the blood plasma in children with RB group I during the period of exacerbation was slightly low, amounting to 1.21 ± 0.41 ng/ml compared with indicators in healthy children 1.83 ± 0.21 ng/ ml. While the level of this hormone during the period of remission of the disease turned out to be slightly elevated and amounted to 2.95 ± 0.41 ng/ml

In general, the morphofunctional features of the immune and endocrine systems established in children of group II indicate a decrease in their body's adaptive capabilities to environmental influences and, together with altered immunological reactivity, contribute to the development of severe recurrent inflammatory diseases.

CHAPTER IV THE ROLE OF MAIN POLYMORPHIC VARIANTS OF PRO AND AGAINST-INFLAMMATORY CYTOKINE GENES IN THE DEVELOPMENT OF RECURRENT BRONCHITIS IN CHILDREN

4.1. Analysis of polymorphic markers of pro- and anti-inflammatory cytokine genes with recurrent bronchitis and in children with lymphatic-hypoplastic diathesis. Modernly researcher's data hinted the important function of cytokine gene polymorphism in the evolution of respiratory tract diseases [2,49,55].

Despite the fact different studies of cytokine gene polymorphisms, their presence to the clinical situation and the formation of obstructive bronchitis remains unknown. The association of cytokine gene polymorphism in children with obstructive recurrent bronchitis against the background of LHD in the Uzbek citizens has not been studied.

In this regard, we studied the clinical importance and frequency of distribution of alleles and genotypes of cytokine gene polymorphism in children with recurrent bronchitis against the background of lymphatic-hypoplastic diathesis.

According to the studied polymorphisms of the genes TNF-α (-308) G/A, IL-6 (-174) C/G, IL-1β (-31) T/C, IL-10 (- 592) C/A and IL- 4 (-589) C/T the frequency of occurrence of their alleles and genotypes was analyzed in patients with RB and RB against the background of LGD. The examination included 119 patients with RB, who made up the main group (of which group I included 62 patients with RB and group II RB against the background of LHD); the control group consisted of 110 apparently healthy children.

To evaluate the connected relationship among the rs1143627 polymorphism of the IL-1β gene and the thread of evaluating RB, a differential analysis of the administering of allele and genotype frequencies was carried out under control group of patients. The consequence of the evaluate the set side by side groups are presented in table. 4.1.1. Table 4.1.1. Distribution of frequencies of alleles and genotypes of the T-31C polymorphic locus of the IL-1β gene in RB patients of the general sample and conditionally healthy children of the control group

Alleles and genotypes	important group n=119		Under control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	n	%	n	%						
T	163	68.5	170	77.3	4.4	0.03	1.4	1.020- 1.885	1.6	1.031- 2,375
C	75	31.5	50	22.7						
T/T	59	49.6	68	61.8	3.5	0.1	0.8	0.635- 1.013	0.6	0.359- 1.028
T/C	45	37.8	34	30.9	1.2	0.3	1.2	0.852- 1.757	1.4	0.785- 2.352
C/C	15	12.6	8	7.3	1.8	0.2	1.7	0.765- 3.927	1.8	0.747- 4.525

As we can see from the table, the prevalence of existance of alleles T and C of the IL-1β gene in the general examination was: 68.5% and 31.5% and under control group – 77.3% and 22.7%, separately.

Numerical processing divulged a remarkable increase in the frequency of the unfavorable allele C, which showed a significant association with the disease (RR=1.4; 95% CI: 1.031-2.375, $\chi 2$ =4.4; p=0.03).

Analysis of the distribution of T/T genotypes in the total sample of patients was 48.4%, in the control group 61.8% were recorded. The indicators of the homozygous T/T genotype tended to decrease compared to the control group (RR=0.8; 95% CI: 0.635-1.013, $\chi 2$ =3.5; p=0.1), being a marker of a low risk of developing RB. The frequency of heterozygous carriage of the T/C genotype in the total sample of patients was 38.7%; in the control group, it was 30.9%. Indicators of heterozygous carriage of the T/C genotype in the general sample of patients tended to increase.

At the same time, analysis of the frequency distribution of the C/C genotype of the T-31C polymorphism of the IL-1β gene was 1.7 times increased in the total sample of patients - 12.6%. In the control group, 7.3% were registered (RR=1.7; 95% CI: 0.747-4.525, $\chi 2$ =1.8; p=0.2). The distribution of allele frequencies in patients with RB showed (Table 4.1.2.) that the unfavorable allele C was statistically significantly more often determined in patients with RB (28.2%) and the relative risk of developing pathology was 1.3 than in children of the control group (22.7%; RR=1.2 ; 95% CI: 0.856-1.801, OR=1.3, CI: 0.809-2.2011, $\chi 2$ =1.3; p=0.3), the wild allele T in children of group I was determined less frequently (71.8% p=0.3), compared with conditionally healthy children. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele C in children from the Republic of Belarus increased by 1.3 times, 95% CI 0.809; 2.201.

Table 4.1.2.

Distribution of frequencies of alleles and genotypes of the polymorphic locus T-31C of the IL-1β gene in patients of group I

Alleles and genotypes	Group I n = 62		Control group n=110		χ2	P	R R	95% CI	OR	95% CI
	n	%	n	%						
T	89	71.8	170	77.3	1.3	0.3	1.2	0.856; 1.801	1.3	0.809- 2.201
C	35	28.2	50	22.7						
T/T	33	53.2	68	61.8	1.2	0.3	0.9	0.654- 1.134	0.7	0.374- 1.320
T/C	23	37.1	34	30.9	0.7	0.4	1.2	0.782- 1.841	1.3	0.685- 2.538
C/C	6	9.7	8	7.3	0.3	0.6	1.3	0.484- 3.660	1.4	0.451- 4.135

The frequency of the wild homozygous genotype IL-1β T/T in patients of group I was also detected statistically significantly less often (53.2%) than in conditionally healthy children 61.8% (RR=0.9; 95% CI: 0.654-1.134, OR=0.7 , 95% CI: 0.374-1.320 χ2 =1.2; p=0.3). An increase in the number of homozygous T/T genotype was revealed in children of the control sample, which indicates a possible protective effect of this genotype in relation to the formation of RB. The heterozygous genotype T/C among patients of group I was more common compared to controls, and the odds ratio showed that the chance of detecting this genotype was 1.3 (RR=1.2; 95% CI: 0.782-1.841, χ2 =0.7; OR=1.3; 95 % CI: 0.685-2.538).

Analysis of the frequency distribution of the unfavorable C/C genotype of the T-31C polymorphism of the IL-1β gene in patients of group I was determined quite often (9.7% RR=1.3; 95% CI: 0.484-3.661, OR= 1.4, 95% CI: 0.451-4.135, χ2 =0.3; p=0.6).

In patients with RB against the background of LHD, statistically significant differences were revealed in the distribution of allele frequencies and genotypes of the polymorphic locus -31 T>C of the IL-1β gene, Table. 4.1.3.

All patients with RB against the background of LHD, numerously noticable differences were revealed in the distribution of allele frequencies and genotypes of the polymorphic locus -31 T>C of the IL-1β gene, Table. 4.1.3.

Table 4.1.3.

Distribution of frequencies of alleles and genotypes of the polymorphic locus T-31C of the IL-1β gene in patients with RB against the background of LHD

Alleles and genotypes	Group II n = 75		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
T	74	64.9	170	77.3	5.83	0.01	1.5	1.089-2.188	1.8	1.118- 3.022
C	40	35.1	50	22.7						
T/T	26	45.6	68	61.8	4.01	0.02	0.7	0.536-1.015	0.5	0.271- 0.990
T/C	22	38.6	34	30.9	1.00	0.3	1.2	0.812-1.920	1.4	0.72- 2.744
C/C	9	15.8	8	7.3	2.98	0.1	2.2	0.885-5.324	2.4	0.869- 6.579

The critical allele C was statistically identified more in patients of group II (35.1%) and the risk factor for pathology was 1.5 time higher in children within control group (22.7%; RR=1.5; 95% CI: 1.089-2.188, χ2 =5.83; p= 0.01), the wild allele T in children of group II was determined significantly less frequently (64.9% p = 0.02) compared to conditionally healthy children. The estimated percent ratio indicated that the chance of detecting a functional unfavorable allele C in children of group II increased by 1.8 times 95% CI 1.118; 3.022.

The action of wild homozygous IL-1β T/T genotype in patients of 2 group were identified as significantly more reliable (45.6%) than healthy children 61.8% (RR=0.7; 95% CI: The heterozygous genotype T/C among patients of group II was more common compared to controls, and the odds ratio showed that the chance of detecting this genotype was 1.4 (RR=1.2; 95% CI: 0.812-1.920, χ2 =1.0; OR=1.4; 95 % CI: 0.720-2.744).effect of this genotype in relation to the formation of RB against the background of LHD.

The heterozygous genotype T/C among patients of group II was more common compared to controls, and the odds ratio showed that the chance of detecting this genotype was 1.4 (RR=1.2; 95% CI: 0.812-1.920, χ2 =1.0; OR=1.4; 95 % CI: 0.720-2.744).

Analyzing the density of the unfavorable C/C genotype of the T-31C polymorphism of the IL-1β gene in patients of group II was determined

significantly more often (15.8% RR=2.2; 95% CI: 0.885-5.324, $\chi 2$ =2.98; p=0.05).

In patients with RB against the backup of LHD, the IL-1β C/C genotype were 2.2 time higher than the percentage of humans with exact same genotype in children out of the control group p <0.05, which more looking like indicates a tendency towards association of this genotype with the -31T polymorphic locus >C IL-1β gene with disease.

Thus, the results of the study suggest that the polymorphic variant of the T31C locus of the IL-1β gene is a marker of the risk of evaluating of RB in children with LHD in the Uzbek nation .Evaluation of the personal risk of establishing RB opposed to the LHD, relying upon recognizing the genetic characteristics of patients, will allow optimizing the implementation of treatment and preventive measures.

Anti-inflammatory IL-4, a product of the Th2 phenotype CD4, acts as an antagonist of Th1-related cytokines and thus contributes to the polarization of the humoral immune response. [91,99].

It also controls the proliferation and differentiation of B cells and T helper cells, and the production of immunoglobulin E. [23]. To assess the associative relationship between the rs2243250 polymorphism of the IL-4 gene and the risk of developing RB, a comparative analysis of the distribution of allele frequencies and genotypes of the general sample of sick and apparently healthy control children was carried out. The results of the study in the compared groups are presented in Table 4.1.4.

Table 4.1.4.

Dissemination frequency of alleles and genotypes of the C589T polymorphic locus of the IL-4 gene in patients with RB in the main group and in the control group

Alleles and genotypes	Group I n = 62		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
C	181	76.1	184	83.6	4.1	0.04	1.5	1.006- 2.129	1.6	1.011; 2.562
T	57	23.9	36	16.4						
C/C	71	59.7	78	70.9	3.2	0.1	0.8	0.696- 1.018	0.6	0.350- 1.053
C/T	39	32.8	28	25.5	1.5	0.2	1.3	0.854- 1.941	1.4	0.803- 2.537
T/T	9	7.6	4	3.6	1.6	0.2	2.1	0.659- 6.561	2.2	0.648- 7.254

It is clearly visible through the Table 4.1.5., the recurrence of giving out of alleles C and T of the IL-4 gene in the general sample of patients was: 76.1% and 23.9% and in the control group – 83.6% and 16.4%, respectively.

Statistical processing showed off that significant evaluation in the prevalence of the unfavorable allele T, which showed a significant association with the disease (RR=1.5; 95% CI: 1.006-2.129, $\chi 2$ =4.1; p=0.04). Analysis of the distribution of C/C genotypes in the total sample of patients was 59.7%, in the control group 70.9% were recorded. Indicators of the homozygous genotype C/C tended to decrease compared to the control group (RR=0.8; 95% CI: 0.696-1.018, $\chi 2$ =3.2; p=0.1), being a marker of a low risk of developing RB. The frequency of heterozygous carriage of the C/T genotype in the total sample of patients was 32.8%, in the control group - 25.5%. Indicators of heterozygous carriage of the C/T genotype in the general sample of patients tended to increase.

Analysis of the frequency distribution of the mutant T/T genotype C-589T of the IL-4 gene was 2.1 times increased in the total sample of patients - 7.6% versus 3.6% (RR=2.1; 95% CI: 0.659-6.561, $\chi 2$ =1.6; p=0.2).

Table 4.1.5.

Distribution frequency of alleles and genotypes of the C589T polymorphic locus of the IL-4 gene in patients of group I and in the control group

Alleles and genotypes	Group I n = 62		Control group n=110		$\chi 2$	P	RR	95% CI	OR	95% CI
	N	%	n	%						
C	102	82.3	184	83.6	0.1	0.7	1.1	0.669- 1.757	1.1	0.615- 1.975
T	22	17.7	36	16.4						
C/C	43	69.4	78	70.9	0.05	0.8	1.0	0.797- 1.223	0.9	0.471- 1.831
C/T	16	25.8	28	25.5	0.003	0.96	1.0	0.597- 1.722	1.0	0.50 - 2.077
T/T	3	4.8	4	3.6	0.1	0.7	1.3	0.308- 5.754	1.3	0.292- 6.226

The distribution of alleles C and T of the IL-4 gene in group I was: 82.3% and 17.7%, in the control group – 83.6% and 16.4%, respectively (Table 4.1.5). Statistical processing evaluates a tendency towards an increase in the frequency of the unfavorable allele T in patients of group I (RR=1.1; 95% CI: 0.669-2.129, $\chi 2$ =0.1; p=0.7). (Table 4.1.5.

Analyzing of the essentials of C/C genotypes in group I of patients was 69.4%, in the control group 70.9%. Indicators of the homozygous C/C genotype tended to decrease compared to the control group (RR=1.0; 95% CI: 0.797-1.2, $\chi 2$ =0.05; p=0.1). The frequency of heterozygous carriage of the C/T genotype in group I patients was 25.8%; in the control group, 25.5%. The indicators of heterozygous carriage of the C/T genotype did not have statistically significant differences. At the same time, the analysis of the frequency distribution of the T/T genotype of the C-589T polymorphism of the IL-4 gene in group I was 4.8%, in the control group - 3.6% (RR=1.3; 95% CI: 0.308-5.754, $\chi 2$ =0.1; p=0.7).

Table 4.1.6.

Frequency of distribution of alleles and genotypes of the polymorphic locus C589T of the IL-4 gene in patients in group II and controls.

Alleles and genotypes	Group II n = 57		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	n	%	n	%						
C	79	69.3	184	83.6	9.22	0.002	1.9	1.249-2.817	2.3	1.327- 3.865
T	35	30.7	36	16.4						
C/C	28	49.1	78	70.9	7.69	0.01	0.7	0.518-0.926	0.4	0.204- 0.768
C/T	23	40.4	28	25.5	3.93	0.05	1.6	1.011-2.484	2.0	1.002- 3.915
T/T	6	10.5	4	3.6	3,17	0,1	2.9	0.851-9.845	3.1	0.842-11.537

The prevalence giving of alleles C and T of the IL-4 gene in group II of patients was: 69.3% and 30.7% and inside control group – 83.6% and 16.4%, individually (Table 4.1.6.). Statistical processing revealed a significant increase in the frequency of the unfavorable T allele, which showed a significant association with the disease (RR=2.9; 95% CI: 0.851-9.845, $\chi 2$ =9.22; p=0.002). Analysis of the distribution of the homozygous genotype C/C also showed a significant decrease in group II of patients compared to the control group (RR=0.7; 95% CI: 0.518-0.926, $\chi 2$ =7.69; p=0.01), was an indicator of a high risk of developing RB in children with LHD. The prevalence of heterozygous transporter of the C/T genotype in patients of group II was 40.4% in control group - 25.5%. exposed of heterozygous carriage of the C/T

genotype had a significant increase in patients of group II (OR=2.0; 95% CI: 1.002-3.915, $\chi 2$ =3.93; p=0.05). While studying the distribution analysis of the frequency distribution of the mutant T/T genotype of the C-589T polymorphism of the IL-4 gene, it was almost 3 times increased in the group of patients with RB against the background of LHD - 10.5% versus the control group 3.6%, respectively (RR=2.9; 95% CI: 0.851- 9.845, $\chi 2$ =3.17; p=0.1).

Thus, the results of the study suggest that the polymorphic variant of the C589T locus of the IL-4 gene is a risk marker for the development of RB in children with LHD in the Uzbek population. The cluster of genes encoding the proinflammatory cytokine TNF-α is located on the short arm of chromosome 6 (6p21.1 – 6p21.3) [142].

To date, several functional polymorphic loci have been identified [52,55], among which the most significant is the guanine to adenine substitution variant rs1800629 (G308A).

A study of the frequency distribution of alleles and genotypes of the G308A polymorphism of the TNF-α gene is presented in Table. 4.1.7.

Table 4.1.7.

Distribution of frequencies of alleles and genotypes of the polymorphic locus G-308A of the TNF-α gene in BC patients of the general sample and in the control group

Alleles and genotypes	Group I n = 62		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
G	215	90.3	204	92.7	0.8	0.4	1.3	0.721-2.448	1.4	0.701- 2.655
A	23	9.7	16	7.3						
G/G	96	80.7	94	85.5	0.9	0.3	0.9	0.840-1.061	0.7	0.353- 1.429
G/A	23	19.3	16	14.5	0.9	0.3	1.3	0.742- 2.38	1.4	0.712- 2.830
A/A	0	0	0	0	-	-	-	-	-	-

As can be seen from table 4.1.7. The frequency of occurrence of the wild G allele of the TNF-α gene in the group of the general sample and control was statistically insignificant and amounted to 90% and 92.7%.

The unfavorable allele rs1800629 A was rare and was found in 7.3% of the control group and 10% of the main group of patients. Allele A was 1.4 times higher in the main group. When carrying out statistical processing, despite minor differences, a high odds ratio for detecting an unfavorable allele A in patients with RB in the general sample was revealed (OR=1.4; 95% CI: 0.701-2.655, $\chi 2$ =0.8; p=0.4). The relative risk of developing pathology was 1.3 with a confidence interval of 95% CI: 0.721-2.448. The frequency of the homozygous genotype G/G in the general sample of patients was lower and amounted to 80.7%; in the control group it was 85.5%. The frequency of the G/A genotype in the main group of patients was 19.3%, in the control group it was 14.5%. Indicators of heterozygous carriage of the G/A genotype in the main group of patients tended to increase, which constituted a risk of development in relation to RB (OR=1.4; 95% CI: 0.7-2.83, $\chi 2$ =0.9; p=0.3). The frequency distribution of the unfavorable genotype A/A was not found in any of the groups when analyzed in both study groups.

The adverse allele A was remarkable more repeatedly detected in patients of group I (8.9%) and the comparable risk of developing pathology was 1.4 than in children of the control group (7.3%; RR=1.2; 95% CI: 0.585-2.545, $\chi 2$ =0.3; p= 0.6), while the wild allele G in children of group I was detected less frequently in 91.1%, compared to 92.7% in almost healthy children. computed odds proportion showed that the chance of detecting a functional unfavorable allele A in children of the Republic of Belarus increased by 1.2 times, 95% CI 0.557-2.766. (Table 4.1.8.

Table 4.1.8.

Differences in the frequency of occurrence of alleles and genotypes of the G308A gene of the TNFα I group of patients and the control sample

Alleles and genotypes	Group I n= 62		Control group n=110		$\chi 2$	P	RR	95% CI	OR	95% CI
	N	%	n	%						
G	113	91.1	204	92.7	0.3	0.6	1.2	0.585- 2.545	1.2	0.557- 2.766
A	11	8.9	16	7.3						
G/G	51	82.3	94	85.5	0.3	0.6	1.0	0.838- 1.106	0.8	0.341- 1.828
G/A	11	17.7	16	14.5	0.3	0.6	1.2	0.605- 2.461	1.3	0.547- 2.935
A/A	0	0	0	0	-	-	-	-	-	-

The frequency of the wild homozygous genotype G/G of the TNF-α gene in patients of group I was lower than in conditionally healthy children (82.3%

versus 85.4%, respectively, with RR=1.0; 95% CI: 0.838-1.106, χ2 =0.4; p=0.6). An increase in the number of homozygotes of the G/G genotype in children of the control group indicates a possible protective effect of this genotype regarding the formation of RB.

The heterozygous genotype G/A among patients of group I was more common compared to controls, and the odds ratio showed that the risk of developing RB in the presence of this genotype increases by 1.2 times (OR=1.3; 95% CI: 0.547-2.935, χ2 =0.3).

In patients of group II, statistically significant differences were revealed in the distribution of alleles and genotype frequencies of the polymorphic locus G308A of the TNF-α gene. (Table 4.1.9.

Table 4.1.9.

Distribution of frequencies of alleles and genotypes of the polymorphic locus G308A of the TNF-α gene in RB patients of the main groups

Alleles and genotypes	Group II n=57		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
G	102	89.5	204	92.7	1.03	0.3	1.4	0.709- 2.954	1.5	0.684- 3.29
A	12	10.5	16	7.3						
G/G	45	79	94	85.4	1.14	0.3	0.9	0.791- 1.078	0.6	0.279- 1.462
G/A	12	21	16	14.5	1.14	0.3	1.4	0.736- 2.847	1.6	0.684- 3.588
A/A	0	0	0	0	-	-	-	-	-	-

The distribution of allele frequencies in patients with RB against the background of LHD showed an increase in the unfavorable allele A in patients of group II (10.5%) and the relative risk of developing pathology was 1.4 than in children of the control group (7.3% ; RR=1.4; 95% CI: 0.709; 2.954, χ2 =1.03; p=0.3), while the wild allele G in children of group II was detected less frequently in 89.5%, compared to 92.7% in conditionally healthy children. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele A in children of group II increased by 1.5 times, 95% CI 0.684-3.29.

As can be seen from table 4.1.7. the frequency of the wild homozygous genotype G/G of the TNF-α gene in patients of group II was lower than in conditionally healthy children (79% versus 85.4%, respectively, with RR=0.9; 95% CI: 0.791-1.078, χ2 =1.14; p <0.3). An increase in the number of

homozygous G/G genotype in children of the control group indicates a possible protective effect of this genotype regarding the formation of RB against the background of LGD. The heterozygous genotype G/A among patients in group II was more common compared to controls, and the odds ratio showed that the risk of developing RB against the background of LGD in the presence of this genotype increases by 1.4 times (OR=1.6; 95% CI: 0.684-3.588, $\chi 2$ =1.14).

It is known from the literature that the polymorphic variant for alleles and genotypes of the G-308A polymorphism of the TNF-α gene is characterized by some frequency differences between ethnic groups [77, 126, 145,150, 158, 176]. According to these data, for Mongoloids, the frequency of occurrence of the unfavorable genotype A/A is 0-2% [79]. This is confirmed by our study, which showed that in all studied groups there were no cases of carriage of A/A genotypes of the TNF-α gene.

Thus, the results of the study indicate that the G-308A polymorphism of the TNF-α gene affects the level of tumor necrosis factor alpha in the blood of patients with RB on the background of LHD. This shows that the acute immune inflammatory process persists longer in patients of group II and can transform into a chronic pathology.

The gene encoding IL-6 is located on chromosome seven in the 7p21-p14 region, which contains five exons.

In the IL-6 C174G promoter region, the C allele (cytosine) is replaced by the G allele (guanine). It is known that the presence of the G allele causes a high level of circulating IL-6 in the blood of patients [76]. IL-6 stimulates activation of the vascular endothelium, proliferation of smooth muscle cells and induces leukocytes.

To appraise the coincidental relations between the rs18000795 polymorphism of the IL-6 gene and higher risk of creating chance to RB, a comparative analysis of the distribution of allele and genotype frequencies was carried out in the learned groups of children and controls. The results of the study in the compared groups are presented in table. 4.1.10.

Table 4.1.10

Distribution of frequencies of alleles and genotypes of the C174G polymorphic locus of the IL-6 gene in groups of RB patients of the general sample and control

Alleles and genotypes	Main group n=119		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
C	185	77.7	181	82.3	1.5	0.2	1.3	0.867- 1.820	1.3	0.838-2.109
G	53	22.3	39	17.7						
C/C	74	62.2	75	68.2	0.9	0.3	0.9	0.755- 1.102	0.8	0.444-1.325
C/G	37	31.1	31	28.2	0.2	0.6	1.1	0.739- 1.647	1.1	0.651-2.030
G/G	8	6.7	4	3.6	1.1	0.3	1.8	0.573- 5.968	1.9	0.559-6.530

As can be seen from the table, the frequency of distribution of alleles C and G of the IL-6 gene in patients with recurrent bronchitis in the general sample was: 77.7% and 22.3%, in the control group 82.3% and 17.7%, respectively. The observed distribution of allele frequencies for the C174G polymorphism of the IL-6 gene in the groups of patients with RB and the control group revealed statistically insignificant differences (p = 0.2). At the same time, the chance of detecting the G allele was OR=1.3; 95% CI: 0.838–2.10.

Analysis of the distribution of C/C genotypes in the total sample of patients was 62.2%; in the control group, 68.2% was recorded. Indicators of the homozygous genotype C/C decreased compared to the control group (RR=0.9; 95% CI: 0.867-1.820, $\chi 2$ =1.5; p=0.2), being a marker of a low risk of developing RB. The frequency of heterozygous carriage of the C/G genotype in the total sample of patients was 31.1%; in the control group it was 28.2%. The distribution of frequencies of heterozygous carriage of the C/G genotype and the mutant G/G genotype did not reveal statistically significant differences (p=0.5) Table 4.1.11. Therefore, this polymorphism is not a marker of susceptibility to RB.

Table 4.1.11.

Distribution of frequencies of alleles and genotypes of the C174G polymorphic locus of the IL-6 gene in groups of patients with RB and controls

Alleles and genotypes	I-group n=62		Control group n=110		χ2	P	RR	95% CI	OR	95% CI
	n	%	n	%						
C	98	79	181	82.3	0,5	0.5	1.2	0.758- 1.845	1.2	0.708- 2.142
G	26	21	39	17.7						
C/C	41	66.1	75	68.2	0,1	0.8	1.0	0.779- 1.208	0.9	0.47- 1.765
C/G	16	25.8	31	28.2	0,1	0.7	0.9	0.546- 1.535	0.9	0.438- 1.793
G/G	5	8.1	4	3.6	1,6	0.2	2.2	0.618- 7.956	2.3	0.62- 9.345

As can be seen from Table 4.1.10., the distribution of alleles C and G of the IL-6 gene in patients with RB was: 79% and 21% and in the control group 82.3% and 17.7%, respectively.

Statistical processing revealed an insignificant increase in the frequency of the unfavorable allele G in patients with RB, while the relative risk of developing pathology was 1.2 times (RR=1.2; 95% CI: 0.758-1.845, $\chi 2$ =0.5; p=0.5).

Analysis of the distribution of C/C genotypes in the group of patients with recurrent bronchitis was 66.1%, in the control group it was 68.2%. Indicators of the homozygous genotype C/C decreased compared to the control group (RR=1.0; 95% CI: 0.546-1.535, $\chi 2$ =0.1; p=0.8). The frequency of heterozygous carriage of the C/G genotype in patients with RB is 25.8%, in the control group 28.2%. Indicators of the heterozygous genotype C/G decreased compared to the control group. (RR=0.9; 95% CI: 0.779-1.208, $\chi 2$ =0.1; p=0.7).

However, it should be noted that the homozygous G/G genotype in patients with RB, which was 2.2 times higher compared to the control group (RR=2.2; 95% CI: 0.618-7.956, $\chi 2$ =1.6; P=0.2) is a genetic risk factor for the development of the disease in children of group I.

Table 4.1.12.

Distribution of frequencies of alleles and genotypes of the C174G polymorphic locus of the IL-6 gene in groups of patients with RB against the background of LHD and controls

Alleles and genotypes	II - group n=57		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
C	89	78.1	181	82.3	0.86	0.4	1.2	0.790-1.937	1.3	0.743- 2.288
G	25	21.9	39	17.7						
C/C	33	57.9	75	68.2	1.74	0.2	0.8	0.658- 1.096	0.6	0.331- 1,.243
C/G	21	36.8	31	28.2	1.31	0.25	1.3	0.832- 2.055	1.5	0.753- 2.934
G/G	3	5.3	4	3.6	0.25	0.6	1.4	0.335- 6.247	1.5	0.318- 6.815

The distribution of frequencies of alleles C and G of the IL-6 gene in the group of patients in group II and controls was: 78.1% and 21.9% and in the control group 82.3% and 17.7%, respectively. Statistical processing revealed an insignificant increase in the frequency of the unfavorable allele G in patients of group II, while the relative risk of developing pathology was 1.2 times (RR=1.2; 95% CI: 0.790-1.937, $\chi 2$ =0.86; p=0.4). Analysis of the distribution of C/C genotypes in group II of patients was 57.9%, in the control group 68.2% was recorded. Indicators of the homozygous C/C genotype decreased compared to the control group (RR=0.8; 95% CI: 0.658-1.096, $\chi 2$ =1.74; p=0.2). The frequency of heterozygous carriage of the C/G genotype in patients of group II was 36.8%, in the control group 28.2%. Indicators of the heterozygous genotype C/G increased compared to the control group. (RR=1.3; 95% CI: 0.832-2.055, $\chi 2$ =1.31; p=0.25). However, it should be noted that the homozygous G/G genotype increased in patients with RB against the background of LHD, which was 1.4 times higher than in the control group (RR=1.4; 95% CI: 0.335-6.247, $\chi 2$ =0.25; p=0.6).

Thus, this polymorphism is not a marker of susceptibility to RB in children with LGD. Although the C allele and the homozygous C/C genotype are protective in the development of the disease.

The gene encoding IL-10 is located on chromosome 1, 1q31-1q32 and consists of five exons and four introns. It has been shown that several important

polymorphic regions in the IL-10 gene, including three in the promoter region (-1082 G/A, -819 C/T, -592 C/A), can influence IL-10 expression [76].

To assess the associative relationship between the rs1800872 polymorphism of the IL-10 gene and the risk of developing RB, a comparative analysis of the distribution of allele and genotype frequencies was carried out in the studied groups of patients and controls. The results of the study in the compared groups are presented in table. 4.1.13.

Table 4.1.13.

Distribution of frequencies of alleles and genotypes of the C592A polymorphic locus of the IL-10 gene in RB patients of the general sample and control

Alleles and genotypes	Main group n=119		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	N	%	n	%						
C	175	73.5	155	70.5	0.5	0.5	0.9	0.668- 1.202	0.9	0.571- 1.292
A	63	26.5	65	29.5						
C/C	65	54.6	56	50.9	0.3	0.6	1.1	0.839- 1.372	1.2	0.69- 1.952
C/A	45	37.8	43	39.1	0.04	0.8	1.0	0.697- 1.343	0.9	0.556- 1.614
A/A	9	7.6	11	10	0.4	0.5	0.8	0.326- 1.755	0.7	0.293- 1.851

As can be seen from table 4.1.12. the frequency of distribution of alleles C and A of the IL-10 gene in the total sample of patients was: 73.5% and 26.5% and in the control group – 70.5% and 29.5%, respectively. Statistical processing revealed a slight decrease in the frequency of the unfavorable allele A (RR=0.9; 95% CI: 0.668-1.202, $\chi 2$ =0.5; p=0.5). Analysis of the distribution of C/C genotypes in the total sample of patients was 54.6%, in the control group 50.9% was recorded. Indicators of the homozygous genotype C/C tended to increase compared to the control group (RR=1.1; 95% CI: 0.839-1.372, $\chi 2$ =0.3; p=0.6), being a low risk factor for the development of RB. The frequency of heterozygous carriage of the C/A genotype in the total sample of patients was 37.8%; in the control group it was 39.1%. Indicators of heterozygous carriage of the C/A genotype in the general sample of patients tended to decrease. Analysis of the frequency distribution of the A/A genotype C592A of the IL-10 gene in the general sample of patients was recorded as 7.6%, versus 10% in the control group (RR=0.8; 95% CI: 0.326-1.755, $\chi 2$ =0.4; p=0.5).

Table 4.1.14.

Distribution of frequencies of alleles and genotypes of the polymorphic locus C592A of the IL-10 gene in patients in group I and controls

Alleles and genotypes	I-group n=62		Control group n=110		χ2	P	RR	95% CI	OR	95% CI
	n	%	n	%						
C	93	75	155	70.5	0.8	0.4	0.8	0.586- 1.221	0.8	0.483- 1.309
A	31	25	65	29.5						
C/C	36	58.1	56	50.9	0.8	0.4	1.1	0.862- 1.509	1.3	0.713- 2.502
C/A	21	33.8	43	39.1	0.5	0.5	0.9	0.570- 1.317	0.8	0.416- 1.530
A/A	5	8,1	11	10	0.2	0.7	0.8	0.294- 2,215	0.8	0.261- 2.387

The distribution of alleles C and A of the IL-10 gene in the group of patients with recurrent bronchitis was: 75% and 25% and in the control group - 70.5% and 29.5%, respectively. Statistical processing revealed a non-significant decrease in the frequency of the unfavorable allele A (RR=0.8; 95% CI: 0.586-1.221, $\chi 2$ =0.8; p=0.4). (Table 4.1.14.

Analysis of the distribution of C/C genotypes in the group of patients with recurrent bronchitis was 58.1%, in the control group it was 50.9%. Indicators of the homozygous C/C genotype in patients tended to decrease compared to the control group (RR=1.1; 95% CI: 0.862-1.509, $\chi 2$ =0.8; p=0.4). The frequency of heterozygous carriage of the C/A genotype in the RB group was 33.8%; in the control group, it was 39.1%. Indicators of heterozygous carriage of the C/A genotype tended to decrease in patients with RB. The frequency of the homozygous A/A genotype in patients was 8.1%; in the control group, it was 10%. Indicators of the homozygous A/A genotype also tended to decrease compared to the control (RR=0.8; 95% CI: 0.294-2.215, $\chi 2$ =0.2; p=0.7).

The frequency of distribution of alleles C and A of the IL-10 gene in patients with RB against the background of LHD was: 71.9% and 28.1% and in the control group – 70.5% and 29.5%, respectively (Table 4.1.15).

Table 4.1.15.

Distribution of frequencies of alleles and genotypes of the polymorphic locus rs1800872 of the IL-10 gene in patients in group II and controls.

Alleles and genotypes	II-group n=57		Control group n=110		χ^2	P	RR	95% CI	OR	95% CI
	n	%	n	%						
C	82	71.9	155	70.5	0.08	0.8	1.0	0.664- 1.359	0.9	0.564- 1.535
A	32	28.1	65	29.5						
C/C	29	50.9	56	50.9	0.0	1.0	1.0	0.73- 1.368	1.0	0.527- 1.894
C/A	24	42.1	43	39.1	0.14	0.7	1.1	0.734- 1.581	1.1	0.591- 2.172
A/A	4	7	11	10	0.41	0.5	0.7	0.234- 2.106	0.7	0.206- 2.237

Statistical processing revealed a tendency towards a decrease in the frequency of the unfavorable allele A (RR=0.8; 95% CI: 0.586-1.221, $\chi 2$ =0.8; p=0.4). Analysis of the distribution of the homozygous genotype C/C in patients of group II and in the control group was 50.9%. The indicators of the homozygous genotype C/C are the same in both groups (RR=1.0; 95% CI: 0.73-1.368, $\chi 2$ =0.1; p=0.1). The frequency of heterozygous carriage of the C/A genotype in patients with RB against the background of LGD was 42.1%; in the control group it was 39.1%. Indicators of heterozygous carriage of the C/A genotype in patients tended to increase. At the same time, analysis of the frequency distribution of the A/A genotype of the C592A polymorphism of the IL-10 gene is reduced in patients with RB against the background of LHD - 7% versus 10% in the control group (RR=0.7; 95% CI: 0.234-2.106, $\chi 2$ =0.41; p=0.5).

Table 4.1.16.

Prognostic effectiveness of IL-10 gene rs1800872 polymorphism

Genetic marker	S_E	S_P	AUC	OR	95%CI	*p
Main group	0.37	0.61	0.49	0.9	0.668-1.202	0.5
Group I	0.34	0.61	0.48	0.8	0.586-1.221	0.4
Group II	0.42	0.61	0.51	1.0	0.664-1.359	0.8

In general, the study of the prognostic effectiveness of the rs1800872 polymorphism of the IL-10 gene shows that the indicators of the level of specificity and sensitivity (SE=0.37) of this locus significantly deviate towards specificity (SP=61). Despite the low OR=0.9, the calculated predictive efficiency of this marker for the total sample was AUC=0.49. Also, in patients of groups I and II, the sensitivity, specificity and prognostic effectiveness of

this locus corresponded to SE = 0.34, SP = 0.61, AUC = 0.48 and SE = 0.42 SP = 0.61 AUC = 0.51 , which may indicate a not very high independent effect of this polymorphism on the risk of developing recurrent bronchitis in the Uzbek population

It has no independent effect on the risk of developing recurrent bronchitis in the Uzbek population.

4.2. Analysis of the association of polymorphic markers of cytokine genes with clinical data in recurrent bronchitis against the background of lymphatic-hypoplastic diathesis.

It should be noted that of particular interest is the assessment of the influence of genetic polymorphism on the clinical course of bronchopulmonary diseases and the severity of the main symptoms characteristic of these pathologies. Knowing the data on the role of gene polymorphism depending on the nature of the disease, one can predict the dynamics of the clinical symptoms of the disease, as well as the formation of relapses or a chronic course of the process. Of the possible individual characteristics of the course of RB and RB against the background of LGD, depending on genetic factors, the association of polymorphism of genes of selected cytokines with such clinical signs as temperature reaction, intoxication and broncho-obstructive syndrome, as well as the duration of exacerbation of recurrent bronchitis was analyzed.

Studying the features of the clinical manifestation of RB against the background of LHD, it was found that in 42% of children with heterozygous genotypes (HT) for the IL-1β gene (T31C), as well as in 8.7% of patients with heterozygous genotypes (GA) for the TNFα gene (G308A) in the clinical course, high body temperature (38-390C) prevailed. In 8.7% of children, a mutant homozygous genotype (CC) for the IL-1β gene (T31C) was identified, in which the temperature reaction was hectic in nature (400 C).

Table 4.2.1.

Frequency of occurrence of alleles and genotypes of the polymorphic locus C-592A of the IL-10 gene, T-31C of the IL-1β gene and C-589T of the IL-4 gene in children of group II.

Genes	Genotypes	Thymomegaly (%)		LGD without thymomegaly (%)
		I degree	II-III degrees	
TNFα (-308)	GA	3.5	17.5	0

	AA	0	0	0
IL-1β (-31)	TC	3.5	10.3	5.3
	CC	0	8.7	0
IL-6 (-174)	CG	14	21	5.3
	GG	0	1.75	0

Of particular interest was the study of the frequency of occurrence of genotypes of the polymorphic locus T-31C of the IL-1β gene and G308A of the TNFα gene in children with thymomegaly.

As can be seen from Figure 4.2.1. the frequency of occurrence of heterozygous T/C and homozygous C/C genotypes of the IL-1β gene and heterozygous G/A gene TNFα was more common in children with thymomegaly. The association of the polymorphic locus T-31C of the IL-1β gene and G308A of the TNFα gene in the heterozygous state was only found in children with grade II-III thymomegaly. These patients had hectic body temperature during the period of exacerbation of the disease (400 C).

When analyzing the association of polymorphism of the cytokine genes IL-1β (T31C), TNFα (G308A), IL-6 (C174G) in 21% of patients with heterozygous genotypes (TC; GA; CG), a high temperature (38-390 C) was detected and noted long-term (30.8±2.2 days) cough. We also established that heterozygous carriage (CG) and mutant homozygous genotype (GG) of IL-6 (C174G) did not occur in isolation

In 15.8% of patients in group II with heterozygous genotypes GA and SA of polymorphic markers of the TNFα (G308A), IL-10 (-592) genes, the relapse of the disease began with subfebrile (37.50 C) body temperature and the duration of exacerbation was 14-18 days

The association between polymorphic variants of the AA genotype polymorphism (-592) of the IL-10 gene, the TC genotype (-31) of the IL-1β gene and the CT genotype (-589) of the IL-4 gene occurred in 17.54% of patients with RB against the background of LHD, in in which severe broncho-obstructive syndrome was noted, and frequent relapses of the disease were also noted. Data analyzes showed that such an association of polymorphic variants of genotypes occurred only in patients with II-III degrees of thymomegaly.

Table 4.2.2.

Frequency of occurrence of genotypes of the polymorphic locus C-592A of the IL-10 gene and T-31C of the IL-1β gene and C-589T of the IL-4 gene in children of group II.

Genes	Genotypes	Thymomegaly (%)			LGD without thymomegaly
		I degree	II degree	III degree	
IL-10 (-592)	CA	1	14%	3,5%	3,5%
	AA	1.75%	1.75%	3.5%	0
IL-1β (-31)	TC	17.5%	14%	1.75%	5.3%
	CC	0	3.5%	8.7%	0
IL-4 (-589)	CT	3.5%	17.5%	10.5%	5.3%
	TT	1.75%	5.3%	3.5%	1.75%

As can be seen from table 4.2.2. the association between genotypes AA of the IL-10 gene and CT/TT of the IL-4 gene was often found in patients with II-III degrees of thymomegaly.

As is known from the literature, the mutation of the IL-10 -592C and IL-4 -589T genes indicates increased protein synthesis of interleukin 10 and 4. This can cause a reduced immune response when exposed to pathogenic factors and increased production of Ig E [91]. This is confirmed by our data, in which the mutant genotypes listed above led to hyperproduction of IgE and broncho-obstructive syndrome.

Studying the features of the clinical manifestation of RD in children of group I, we found that in 4.8% of cases a combination of heterozygous genotypes TC for the IL-1β gene (T31C), SA for the IL-10 gene, CT for the IL-4 gene was found in which the disease worsened repeated 3-4 times a year and patients with these genotypes had a high temperature (38-390 C) Table. 4.2.3.

Table 4.2.3.

Frequency of occurrence of genotypes of polymorphism of cytokine genes in children of group I.

Genes	Genotypes	Control group	Recurrent bronchitis
IL-1β (T31C)	TC	30,9	37,1
	CC	7,3	9,7
IL-6 (C174G)	CG	28,2	25,8
	GG	3,6	8,1*
TNFα (G308A)	GA	14,5	17,7*
	AA	0	0
IL-4 (C589T)	CT	25,5	25,8
	TT	3,6	4,8
IL-10 (C592A)	CA	39,1	33,8
	AA	8,1	10

The association between polymorphic variants of the CA genotype polymorphism (-592) of the IL-10 gene and the GA genotype (-308) of the TNFα gene occurred in 6.45% of patients with RB who had low-grade fever. Also, in 3.22% of patients with the homozygous genotype CC (-T31) of the IL-1β gene, a hectic (390 C) temperature was detected, which lasted for two days.

The association between polymorphic variants of the homozygous genotype CC polymorphism (-T31) of the IL-1β gene, TT (-589) of the IL-4 gene and CG (-308) of the TNFα gene occurred in 11.3% of patients in whom these gene polymorphisms led to private and prolonged exacerbation of the disease. In only one (1.62%) patient, an association was found between the genotypes of all the studied polymorphisms of cytokine genes. In this case, the patient's condition upon admission to the hospital was severe, hectic body temperature and broncho-obstructive syndrome were noted.

Thus, we have established that polymorphic markers of cytokine genes play an important role in shaping the characteristics of the clinical manifestations of recurrent bronchitis and RB in children with LGD. They are

associated with a severe course of the disease, with the presence of severity of broncho-obstructive syndrome, with the temperature reaction of the body, as well as the duration of exacerbation of recurrent bronchitis in children with LGD.

In general, the data presented in the chapter indicate that the genetic marker of the risk of developing RB in children with LGD is the C allele and genotypes TC/CC polymorphism (- 31) of the IL-1β gene, the T allele genotype CT/TT polymorphism (-589) IL-4 gene. The C allele and the CC genotype of polymorphism (-174) of the IL-6 gene are protective in relation to the development of RB against the background of LHD. Polymorphisms of the tumor necrosis factor genes (TNFα -308), IL-10 (-592) are not associated with the development of RB and RB in children with LHD in children in the Uzbek population. Moreover, these polymorphisms have a significant impact on the clinical course of the disease.

4.3. Algorithm for early diagnosis and assessment of the prognostic significance of pro- and anti-inflammatory cytokine genes in the development of recurrent bronchitis in children with lymphatic-hypoplastic diathesis

Based on the results of the research work, an algorithm for early diagnosis and prediction of recurrent bronchitis in children with lymphatic-hypoplastic diathesis was developed

(Fig. 4.3.1).

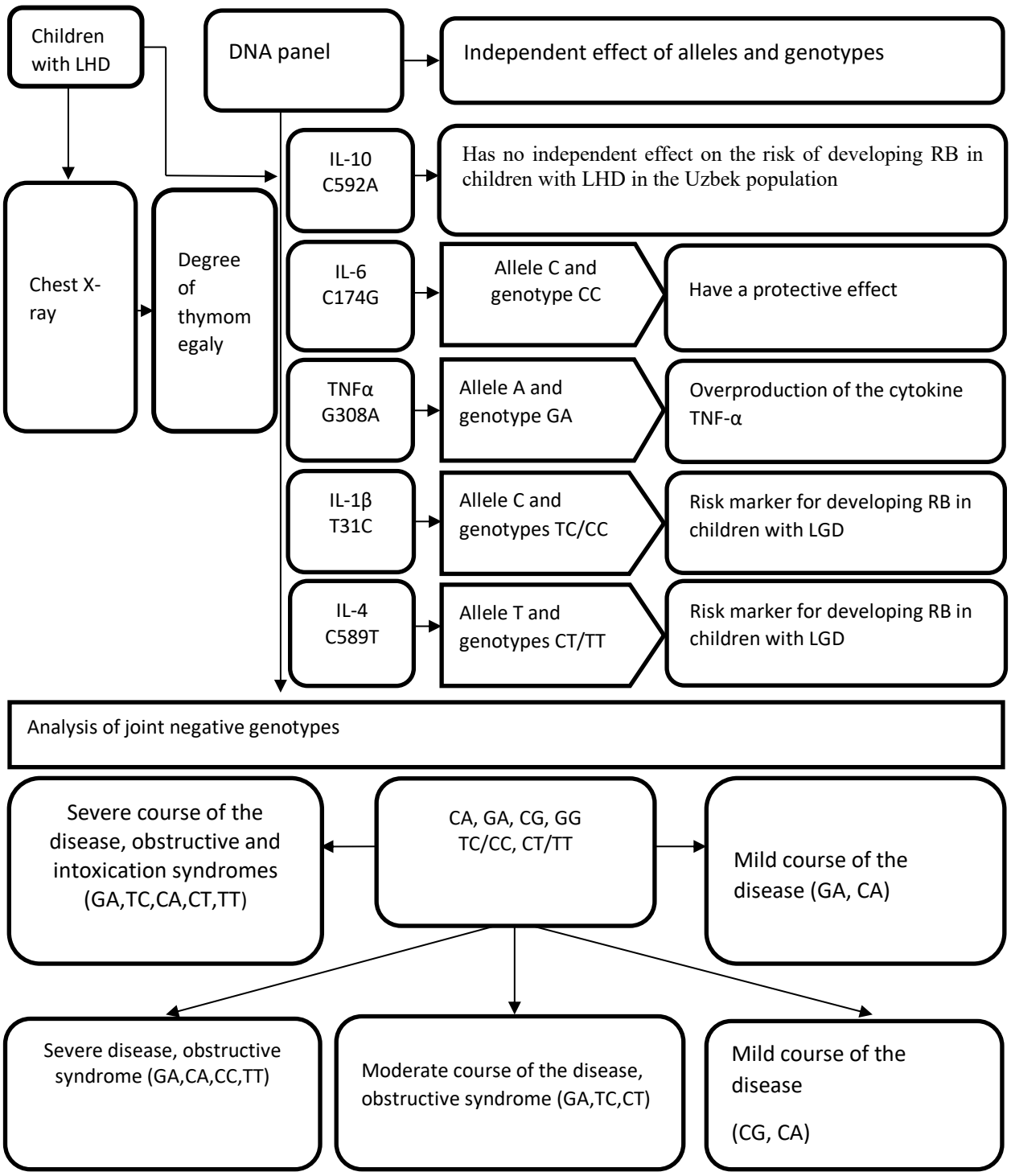
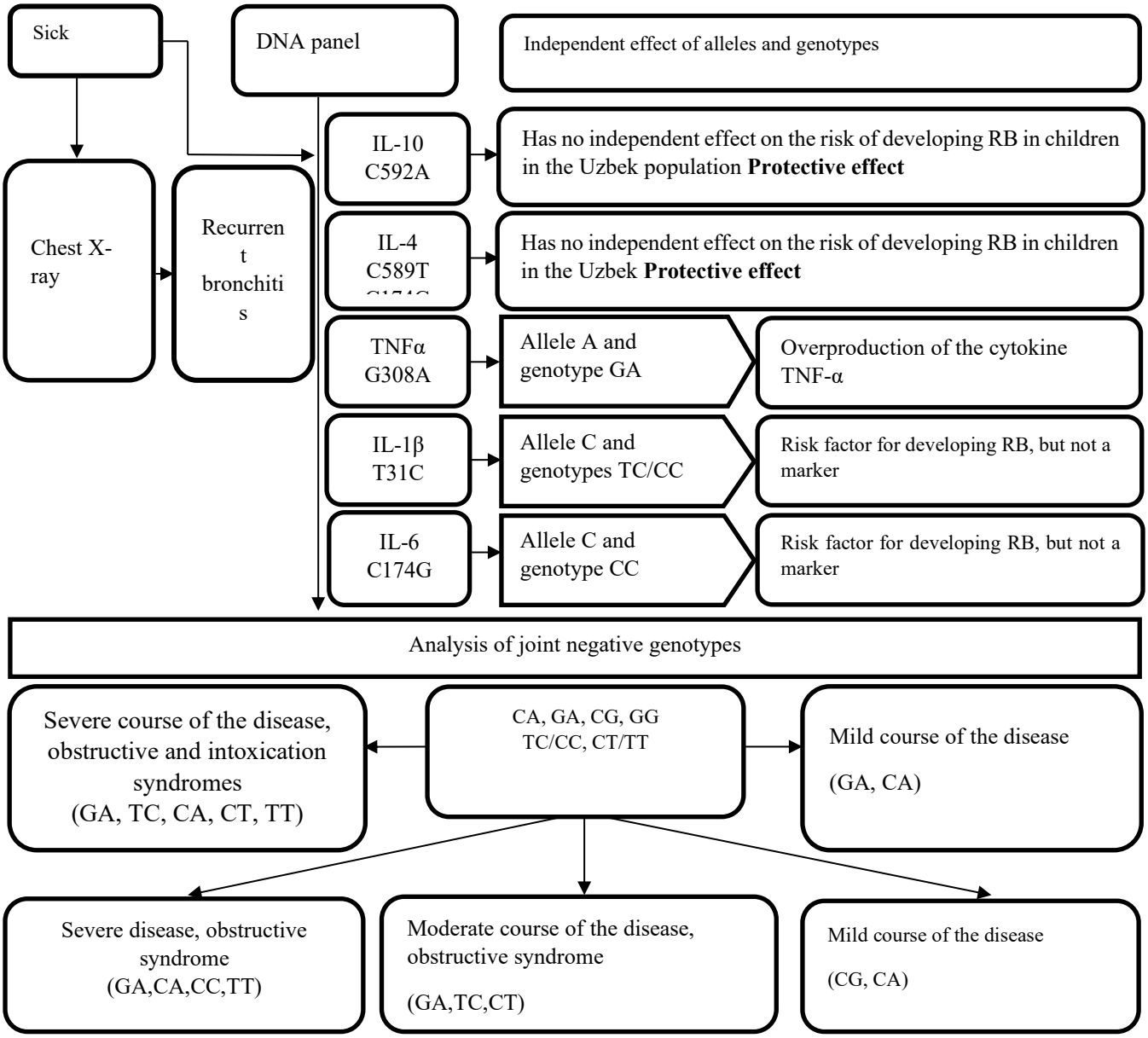


Figure 4.3.1. Algorithm for early diagnosis and prediction of recurrent bronchitis in children with lymphatic-hypoplastic diathesis

Figure 4.3.2.

Algorithm for early diagnosis and prediction of recurrent bronchitis in children



CONCLUSION

Pathology of the respiratory tract in children is a pressing problem in pediatrics and has medical and social significance [5,154,169]. One of the most common nosological forms of respiratory tract damage in children is bronchitis [149

The proportion of bronchitis of a recurrent nature is increasing. Thus, the prevalence of RB among children is currently 2.5 per 1000 children.

One of the important directions in the fight against the occurrence of the disease is aimed at eliminating respiratory diseases in vulnerable children, followed by children of primary prevention. A legitimate question would be about the earliest possible start of preventive measures and, therefore, about the individual nature of the increased risk of developing a particular disease and, as a rule, its transition to a chronic process [57].

Despite the fact that the problem of treatment and prevention of bronchitis in children is well covered in the literature, the genetic basis remains poorly understood. In this regard, it is relevant to identify and study genetic markers in children with RB. Based on modern data on the pathogenesis of respiratory damage in children, the genes of pro- and anti-inflammatory cytokines are candidate genes and are closely related to the development and clinical course of these diseases [88]. In this regard, timely diagnosis of recurrent bronchitis in children, determination of factors contributing to the development of this disease, assessment of immune and hormonal status, determination of the role of pro- and anti-inflammatory cytokines on the course of RB, identification by correlation analysis of the features of the relationship between the polymorphism of cytokine genes and their content serum levels for recurrent bronchitis in children with lymphatic-hypoplastic diathesis are a priority. The work performed presents the results of a clinical, immunological, hormonal, molecular genetic study of 119 children with recurrent bronchitis aged 2 to 7 years. The average age of the examined patients was 4.1±0.82 years. The work was carried out in the children's department of the multidisciplinary clinic of SamState Medical University and in the pulmonology department of the Medical Children's Hospital of Samarkand for the period 2019-2021. All patients were divided into 2 groups: group I included 62 (52%) patients with recurrent bronchitis, of which 35 (56%) were boys and 27 (34%) girls. Group II included 57 (48%) patients with recurrent bronchitis due to LHD, of which 42 (74%) were boys and 15 (26%) girls. The control group consisted of 110 conditionally healthy children of the same age

In patients of the second group, during the initial examination, we paid attention to the external signs of LGD, the condition of the thymus and peripheral lymphoid organs. In 48 (84.2%) patients, pastous habitus was noted, which was usually noted from birth. In 35 (61.4%) patients, birth weight was high with excessive weight and length gain during the first year of life. In patients with RB on the background of LHD, thymomegaly was found in 45 (79%) patients.

Thymomegaly I degree (CTTI 0.33-0.36) was detected in 10 (22.3%) patients, II (CTTI 0.37-0.42) in 22 (40%) and III degree (CTTI 0, 43 and more) - in 17 (37.7%) sick children

In patients of the second group, during the initial examination, we paid attention to the external signs of LGD, the condition of the thymus and peripheral lymphoid organs. In 48 (84.2%) patients, pastous habitus was noted, which was usually noted from birth. In 35 (61.4%) patients, birth weight was high with excessive weight and length gain during the first year of life. In patients with RB on the background of LHD, thymomegaly was found in 45 (79%) patients.

Upon admission to the hospital, 15 (26.32%) patients of group II had a severe general condition, while in patients of group I, in total, it was so in 9 (14.5%).

The main complaints during the exacerbation period in patients of group I were: runny nose, cough, rise in temperature, malaise, loss of appetite. In patients of group II, the main complaints were increased body temperature, cough, expiratory shortness of breath, distant wheezing, weakness, headache, sweating, decreased appetite and sleep disturbance, i.e., intoxication syndrome, DN, and broncho-obstructive syndrome were often accompanied.

In 11 (17.7%) patients of group I, the exacerbation of the disease occurred without an increase in temperature, and in 51 (82.3%) we observed an increase in temperature to subfebrile levels at the beginning of the exacerbation. Whereas, all patients in group II experienced an increase in body temperature (to high temperatures in 21% of children and low-grade fever in 79% of children) at the onset of the disease. Dyspnea was detected in all patients of group II and lasted 3.6±1.4 days, in patients of group I in 26.6% and lasted 2.3±0.6 days $P<0.05$.

The increase in temperature was accompanied by the appearance of a cough. In patients of the first group, a dry cough was mainly observed, and in

16 (25.8%) patients, from 2-4 days, it transformed into a wet cough. While 45 (78.9%) patients in group II had a wet cough.

Thus, children of group I more often had a long-lasting (18.8±4.2) dry cough compared to patients of group II, in whom a wet cough predominated.

In 22 (35%) children of the first group, bronchitis occurred with obstructive syndrome and in 40 (65%) children - as simple bronchitis without obstruction. Whereas in patients of the second group of 57 children, bronchitis occurred in 52 (91.2%) with obstructive syndrome and in only 5 (8.8%) children - in the form of simple bronchitis (without obstruction).

Remission of RB in patients of group II in our observations occurred more slowly: a wet cough persisted for a long time (30 ± 0.06 days), mainly in the morning. Exacerbations were repeated 4-5 times a year with grade I thymomegaly, with grade II thymomegaly 5-6 times and in grade III thymomegaly relapses were repeated 6-8 times a year, while in patients of group I the frequency of relapses was noted 3-4 times a year, in During the inter-relapse period, the children were practically healthy

Early detection of reduced immunological reserves in children is the most important problem of modern pediatrics, the resolution of which will allow for targeted primary prevention of many widespread diseases, including recurrent respiratory diseases [107].

As a result of immunological studies, a more significant suppression of the T-cell immunity in children of the Republic of Belarus against the background of LHD was established - 40.5±1.18% and 48.4±0.96%, respectively ($p<0.001$). The mean values of T-lymphocytes and regulatory subsets were lower in LHD children with thymomegaly than in LHD children without thymomegaly and in healthy children. We also identified a direct correlation between the degree of thymomegaly and the number of leukocytes, lymphocytes ($r = +0.71$; $r = +0.64$), as well as an inverse correlation between the degree of thymomegaly and the number of T-lymphocytes and their subpopulations ($r = - 0.78$; $r = -0.68$; $r = -0.61$). The relative content of T-helper cells had a clear tendency to decrease in patients of both groups compared to healthy children ($p<0.001$). However, a significant decrease in CD4+ content was noted in children of group II (29.7±0.92%) in contrast to patients in group I (32.75±1.28%, $p<0.01$). The CD8+ content in the blood of patients in both groups was reduced compared to the values of children in the control group

($p<0.01$). At the same time, the greatest decrease in CD8+ was detected in patients of group II (20.63±0.51% versus 23.75±0.51% in children of group I, $p<0.001$). When comparing changes in the components of immunity with the degree of thymomegaly, we identified a decrease in the relative number of all T-lymphocytes, also CD8+, as thymomegaly progresses. As is known [35], CD8+ is expressed in humans on mature T lymphocytes. A significant decrease in the CD8+ count in children of group II is probably associated with a decrease in mature T-lymphocytes.

The quantitative imbalance of CD4+ and CD8+ cells led to a change in the immunoregulatory index in patients of both groups, in whom the immunoregulatory index was 1.45±0.04 μl and 1.37±0.08 μl compared to healthy children ($p < 0.05$) .

In patients of group II, in contrast to patients of group I, there was a significant decrease in the CD4+/CD8+ index ($p < 0.01$).

In general, all the data presented above give the idea that in patients with RB on the background of LHD, the immunoregulatory function of T-lymphocytes is more reduced compared to patients with RB without LHD.

When analyzing the CD16+ content, we found a significant increase in this indicator in patients with RB on the background of LHD compared to controls ($p<0.01$); in patients with RB, the content of CD16+ did not differ statistically significantly from similar indicators in Thus, the greatest decrease in the relative content of T-lymphocytes in patients of group II with lymphatic diathesis is associated with a weakening of the migration of T-cells from the thymus to the peripheral part of the immune system, i.e., in these children the processes of differentiation of T-lymphocytes are weakened.

Thus, the greatest decrease in the relative content of T-lymphocytes in patients of group II with lymphatic diathesis is associated with a weakening of the migration of T-cells from the thymus to the peripheral part of the immune system, i.e., in these children the processes of differentiation of T-lymphocytes are weakened.

Analyzing the B-system of immunity and immunoglobulins, we found a significant decrease in B-lymphocytes in patients of group II, while in patients of group I there was a tendency towards an increase in B-lymphocytes.

In sick children in group I, an increase in IgM levels was found in the acute period of the disease compared to healthy children ($P<0.05$), which confirms the fact of infection. Whereas, the level of IgM was significantly low in

patients of group II and amounted to 0.95±0.05 pg/ml, which is apparently associated with the immaturity of B lymphocytes against the background of LHD, since the maturity of B lymphocytes is assessed by the ability to produce immunoglobulins (Ig) [93]. When comparing changes in IgM levels with the degree of thymomegaly, we found a more pronounced decrease in grade III thymomegaly of 0.82±0.065 pg/ml. When studying the concentration of IgA in the blood serum of patients of group I, there was a tendency to reduce the content of IgA compared to the age norm, which indicates the activation of the humoral immunity. But lower IgA content was found in group II patients. In patients of group II, the IgA level was 2.8 times lower than the normative data. In addition, we found an inverse correlation (-0.69) between the level of Ig A and the degree of thymomegaly. The Ig G content tended to decrease in children of the first group, while in patients of the second group there was a significant decrease in the level of IgG, respectively 11.4±0.41 pg/ml and 8.87±0.38 pg/ml ($p<0.05$). A decrease in serum IgG levels in children of group II may be associated with a disruption in the process of switching the synthesis of IgG isotypes, as well as the formation of memory B cells.

IgE levels were high in patients of both groups ($p<0.05$). At the same time, in patients of the second group with thymomegaly II, III degrees, the IgE level turned out to be more elevated compared to healthy children, respectively 44.7±2.3 pg/ml and 30.6±2.3 pg/ml ($p<0.05$).

Thus, with RB in children, the immune response may be either insufficient for protection, in which case an infectious syndrome of secondary immunodeficiency develops, or excessively hyperergic, in which case an allergic syndrome of secondary immunodeficiency develops. Our study showed a combination of these syndromes in patients with RB against the background of LHD.

All of the above says that with RB in children, there is dysregulation of both the cellular and humoral components of the immune response, the mechanisms of which are obviously associated with the activation of pro-inflammatory cytokines and the immunoregulatory effect of cytokines on T-helper cells type 1 and 2, and this is confirmed by literature data [36] .

As is known [94,95], the key cytokines in the development and maintenance of airway inflammation are mediators such as IL-1β, TNF-α, IL-4, IL-6 and IL-10. Cytokines have a wide range of biological activities and contribute to cell-cell interactions during the immune and inflammatory response [94]. They function as mediators of the immune system, regulate the

strength and duration of the immune response, and determine the type and intensity of the inflammatory process [94,113].

The study of the characteristics of the production of cytokines TNF-α, IL-4, IL-1β, IL-6, IL-10 and the study of the mechanisms of action in recurrent bronchitis in children showed that in children with RB and RB against the background of LHD the production of pro- and anti-inflammatory cytokines significantly ($p<0.001$) increased compared to healthy children

In patients with RB against the background of LHD, the rate of IL-1β production was significantly ($p<0.01$) increased to 46.54±4.27 pg/ml, which was 8.5 times higher than the norm. In patients of group I, this cytokine was 4.2 times higher compared to healthy children. When studying the production of IL-1β depending on the degree of thymomegaly, we established a higher level of IL-1β with thymomegaly of degrees II, III compared to children of degree I, respectively 58.62±6.27 pg/ml and 38.78±4 .34 pg/ml ($p<0.001$). It is known that IL-1β is the first to be included in the body's defense response to pathogenic factors [167]. This cytokine plays a key role in the development and regulation of nonspecific defense and specific immunity, and also regulates inflammatory and immune processes, activates neutrophils, T- and B-lymphocytes [168].

Our work shows that in children with RB, an increase in the production of IL-1β leads to an increase in the proliferative response and endogenous activation of T cells. In patients of group II, the level of the proliferative response to mitogen is weakened and the release of mature T cells from the thymus is weakened, which apparently leads to T lymphopenia. In patients with stage II-III thymomegaly, the deficiency of the T-cell component of the immune system increased, and could contribute to the manifestation of its failure.

When assessing the production of IL-10, we found that 10 in patients with RB against the background of LHD tended to decrease compared to patients with RB, respectively 36.8±3.06 pg/ml and 23.24±2.93 pg/ ml ($p<0.001$). We know that IL-10 is an antagonist of IL-1β and is an anti-inflammatory cytokine. It is the ratio of the levels of these cytokines that most fully reflects the direction of the immune response and the activity of inflammation [167]. Our data show that in patients of group II, the inflammation process is more severe.

There is a natural increase in the anti-inflammatory cytokine IL-4 in all examined groups, but it is more pronounced in patients of group I, exceeding the norm by 4 times. Apparently, this can be explained by the fact that in

patients of group I, the proliferation and differentiation of B cells and antibody genesis are more preserved compared to group II.

When assessing the level of IL-6 in patients of group II, a significant increase in IL-6 was found compared to the group of apparently healthy children and group I, respectively 51.47±3.50 pg/ml; 6.6±0.81pg/ml and 26.28±2.66 ($p<0.001$), which suggests a more severe clinical course of recurrent bronchitis against the background of LHD is more severe compared to group I.

In general, studying the role and significance of pro- and anti-inflammatory cytokines makes it possible to find out that in children RB occurs against the background of immunodeficiency and the reserve capabilities of immunocompetent cells in response to the action of the pathogen are greater in patients of group I. In patients of group II, an imbalance in the immune system leads to a decrease in their overall resistance to infectious agents.

It is known that the thymus gland is a “switchboard” in the interaction between the neuroendocrine and immune systems [14]. In this regard, there was a need to study the basal levels of ACTH, STH and cortisol in children with RB and RB against the background of LHD.

The results of studies of hormone levels in patients showed that during the period of remission there was a slight increase in the concentration of cortisol and growth hormone and an almost two-fold decrease in ACTH in children of the second group. The ACTH/cortisol ratio decreased by almost half and amounted to 0.031 versus 0.058 in healthy people.

In patients of group II during the period of exacerbation of the disease, we found a higher level of growth hormone (5.13 ± 0.79 ng/ml) and low ACTH (5.33 ± 1.37 pmol/l) with an unreliable decrease in cortisol levels (170.9 ±10.36 nmol/l). A study of the content of cortisol, ACTH and GH in children with thymomegaly II-III degree revealed a compensatory increase in cortisol levels to 316±24.6 nmol/l, a more significant decrease in ACTH (5.12±1.21 pmol/l) and 2 times GH level exceeding normative data (4.02±0.4 ng/ml). The ACTH/cortisol ratio was only 0.016, which is 2.37 times lower than physiological.

It is known that steroid hormones weaken the production of thymulin, inhibit the synthesis of specific antibodies, and inhibit the migration of lymphocytes from the intravenous fluid [71]. This is confirmed by our study,

which showed that in patients with RB with stage II-III thymomegaly, during an exacerbation of the disease, an increase in cortisol levels leads to an increase in immunodeficiency.

In patients of group I, it was found that the level of ACTH (20.2±4.9 pmol/l, $p < 0.05$) and cortisol in the blood plasma (367±15.28 ng/ml $p < 0.01$) during the exacerbation period RB significantly increased compared to the group of healthy children, with subsequent normalization of ACTH in the absence of exacerbation of the disease, despite the absence of changes in cortisol levels.

Thus, we base our study on ACTH levels that stimulate cortisol production during the stress of exacerbation of illness, increasing compensation. At this time, the feedback principle does not work well. During remission of RB, free hormone levels decrease with increasing affinity of the transcortin protein for cortisol, while total cortisol levels may increase. At this stage of the disease, the feedback mechanism begins to be fully realized.

Thus, the morphofunctional characteristics of the immune and endocrine systems of the body, established in children of group II, reduce adaptation capabilities to environmental influences and change immunological reactivity and can lead to severe or recurrent inflammatory diseases and immunopathological reactions.

Modern scientific data indicate the important role of cytokine gene polymorphism in the development of respiratory tract diseases [49,55].

Despite the numerous studies of cytokine gene polymorphisms, their contribution to the clinical course and the formation of recurrent bronchitis remains unclear. The association of cytokine gene polymorphism in children with recurrent bronchitis against the background of LGD in the Uzbek population has not been studied.

In this regard, we studied the clinical significance and frequency of distribution of alleles and genotypes of cytokine gene polymorphism in children with recurrent bronchitis against the background of lymphatic-hypoplastic diathesis.

According to the studied polymorphisms of the genes TNF-α (-308) G/A, IL-6 (-174) C/G, IL-1β (-31) T/C, IL-10 (- 592) C/A and IL- 4 (-589) C/T the frequency of occurrence of their alleles and genotypes was analyzed in patients with RB and RB against the background of LGD in children. The examination included 119 patients with RB, who made up the main group (of which group

I included 62 patients with RB and group II RB against the background of LHD); the control group consisted of 110 apparently healthy children.

To assess the associative relationship between the rs1143627 polymorphism of the IL-1β gene and the risk of developing RB, a comparative analysis of the distribution of allele and genotype frequencies was carried out in the studied groups of patients and controls. The results of the study in the compared groups are presented as follows: the frequency of distribution of alleles T and C of the IL-1β gene in the general sample was: 68.5% and 31.5% and in the control group – 77.3% and 22.7%, respectively.

Statistical processing revealed a significant increase in the frequency of the unfavorable allele C, which showed a significant association with the disease (RR=1.4; 95% CI: 1.02-1.885, OR=1.6, 1.031-2.375, $\chi 2$ =4.4; p= 0.03).

Analysis of the distribution of T/T genotypes in the total sample of patients was 49.6%, in the control group 61.8% were recorded. Indicators of the homozygous T/T genotype tended to decrease compared to the control group (RR=0.8; 95% CI: 0.635-1.013, OR=0.6, 0.359-1.028, $\chi 2$ =3.5; p=0.1), being a marker of low risk of developing RB. The frequency of heterozygous carriage of the T/C genotype in the total sample of patients was 37.8%; in the control group, it was 30.9%. Indicators of heterozygous carriage of the T/C genotype in the general sample of patients tended to increase. At the same time, analysis of the frequency distribution of the C/C genotype of the T-31C polymorphism of the IL-1β gene was 1.7 times increased in the total sample of patients – 12.6%. In the control group, 7.3% were registered (RR=1.7; 95% CI: 0.765-3.927, OR=1.8, 0.747-4.525 $\chi 2$ =1.8; p=0.2).

The unfavorable allele C was statistically significantly more often detected in patients with RB (28.2%) and the relative risk of developing pathology was 1.5 than in children of the control group (22.7%; RR=1.2; 95% CI: 0.856-1.801, OR=1.3, CI: 0.809 -2.2011, $\chi 2$ =1.3; p=0.3), the wild allele T in children of group I was determined significantly less frequently (71.8% p=0.3) compared to conditionally healthy children. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele C in children from the Republic of Belarus increased by 1.3 times, 95% CI 0.809; 2.201.

The frequency of the wild homozygous genotype IL-1β T/T in patients of group I was also detected statistically significantly less often (53.2%) than in conditionally healthy children 61.8% (RR=0.9; 95% CI: 0.654-1.134, OR=0.7 , 95% CI: 0.374-1.320 $\chi 2$ =1.2; p=0.3). A significant increase in the number of T/T homozygotes was revealed in children of the control sample, which

indicates a possible protective effect of this genotype in relation to the formation of RB.

The heterozygous genotype T/C among patients of group I was more common compared to controls, and the odds ratio showed that the chance of detecting this genotype was 1.3 (RR=1.2; 95% CI: 0.782-1.841, $\chi 2$ =0.7; OR=1.3; 95 % CI: 0.685-2.538).

Analysis of the frequency distribution of the unfavorable C/C genotype of the T-31C polymorphism of the IL-1β gene in patients of group I was determined significantly more often (9.7% RR=1.3; 95% CI: 0.484-3.661, OR= 1.4, 95% CI: 0.451-4.135, $\chi 2$ =0.3; p=0.6).

In patients with RB on the background of LHD, statistically significant differences were revealed in the distribution of allele frequencies and genotypes of the polymorphic locus -31 T>C of the IL-1β gene.

The unfavorable allele C was statistically significantly more often determined in patients of group II (35.1%) and the relative risk of developing pathology was 1.5 than in children of the control group (22.7%; RR=1.5; 95% CI: 1.089-2.188, $\chi 2$ =5.83; p= 0.01), the wild allele T in children of group II was determined significantly less often (64.9% p = 0.02), compared with conditionally healthy children. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele C in children of group II increased by 1.8 times 95% CI 1.118; 3.022.

The frequency of the wild homozygous genotype IL-1β T/T in patients of group II was also detected statistically significantly less often (45.6%) than in conditionally healthy children 61.8% (RR=0.7; 95% CI: 0.536-1.015, $\chi 2$ =4.01 ; p=0.01). A significant increase in the number of T/T homozygotes was revealed in children of the control sample, which indicates a possible protective effect of this genotype in relation to the formation of RB against the background of LGD.

The heterozygous genotype T/C among patients in group II was more common compared to controls, and the odds ratio showed that the chance of detecting this genotype was 1.4 (RR=1.2; 95% CI: 0.812-1.920, $\chi 2$ =1.0; OR=1.4; 95% CI: 0.720-2.744). Analysis of the frequency distribution of the unfavorable C/C genotype of the T-31C polymorphism of the IL-1β gene in patients of group II was determined significantly more often (15.8% RR=2.2; 95% CI: 0.885-5.324, $\chi 2$ =2.98; $p<0.05$).

When comparing the distribution of frequencies of alleles and genotypes of the polymorphic region -31T>C of the IL-1β gene between patients of the I and II main groups, no significant differences were observed between them. However, in patients with RB against the background of LHD, the IL-1β C/C genotype was 2 times higher than the proportion of individuals with the same genotype in children of group I $p < 0.05$, which probably indicates an existing trend. Association of the genotype of this polymorphic locus - the IL-1β 31T>C gene - with the disease.

The obtained analyzes on the T-31C polymorphism of the IL-1β gene showed a high frequency of occurrence of the mutant allele C among patients of group II compared with the control group. These data allow us to make an assumption about the functional significance of carriage of the -31C allele in the development of RB in children with LGD.

Thus, the results of the study suggest that the polymorphic variant of the T31C locus of the IL-1β gene may be associated with RB disease in children of the Uzbek population. Assessment of the individual risk of developing RB against the background of LGD, based on identifying the genetic characteristics of patients, will allow optimizing the implementation of treatment and preventive measures.

Anti-inflammatory IL-4, a product of the Th2 phenotype CD4, acts as an antagonist of Th1-related cytokines and thus promotes the polarization of the humoral immune response [91,99].

It also controls the proliferation and differentiation of B cells and T helper cells, and the production of immunoglobulin E. [23].

The distribution of alleles C and T of the IL-4 gene in the total sample of patients was: 76.1% and 23.9% and in the control group – 83.6% and 16.4%, respectively.

Statistical processing revealed a significant increase in the frequency of the unfavorable T allele, which showed a significant association with the disease (RR=1.5; 95% CI: 1.006-2.129, $\chi 2 = 4.1$; $p=0.04$). Analysis of the distribution of C/C genotypes in the total sample of patients was 59.7%, in the control group 70.9% were recorded. Indicators of the homozygous genotype C/C tended to decrease compared to the control group (RR=0.8; 95% CI: 0.696-1.018, $\chi 2 = 3.2$; $p=0.1$), being a marker of a low risk of developing RB. The frequency of heterozygous carriage of the C/T genotype in the total sample of patients was 32.8%; in the control group it was 25.5%. Indicators of

heterozygous carriage of the C/T genotype in the general sample of patients tended to increase.

Analysis of the frequency distribution of the mutant T/T genotype C-589T of the IL-4 gene was 2.1 times increased in the total sample of patients – 7.6% versus 3.6% (RR=2.1; 95% CI: 0.659-6.561, $\chi 2$ =1.6; p=0.2).

The distribution of alleles C and T of the IL-4 gene in group I was: 82.3% and 17.7%, in the control group – 83.6% and 16.4%, respectively.

Statistical processing revealed a significant increase in the frequency of the unfavorable T allele, which showed a significant association with the disease (RR=1.1; 95% CI: 0.669-2.129, $\chi 2$ =0.1; p=0.7).

Analysis of the distribution of C/C genotypes in group I of patients was 69.4%, in the control group 70.9%.

The frequency of distribution of alleles C and T of the IL-4 gene in group II of patients was: 69.3% and 30.7% and in the control group – 83.6% and 16.4%, respectively.

Statistical processing revealed a significant increase in the frequency of the unfavorable T allele, which showed a significant association with the disease (RR=2.9; 95% CI: 0.851-9.845, $\chi 2$ =9.22; p=0.002). Analysis of the distribution of the homozygous genotype C/C also showed a significant decrease in group II patients compared to the control group (RR=0.7; 95% CI: 0.518-0.926, $\chi 2$ =7.69; p=0.01), being a marker of a high risk of developing RB. The frequency of heterozygous carriage of the C/T genotype in patients of group II was 40.4% in the control group - 25.5%. Indicators of heterozygous carriage of the C/T genotype had a significant increase in patients of group II (OR=2.0; 95% CI: 1.002-3.915, $\chi 2$ =3.93; p=0.05). When studying the distribution analysis of the frequency distribution of the mutant T/T genotype of the C-589T polymorphism of the IL-4 gene, it was 3.1 times increased in the group of patients with RB against the background of LHD - 10.5% versus the control group 3.6%, respectively (RR=2.9; 95% CI: 0.851-9.845 , $\chi 2$ =3.17; p=0.1).

In patients of group II, statistically significant differences were revealed in the distribution of allele frequencies and genotypes of the polymorphic locus -589 C>T of the IL-4 gene.

Thus, the results of the study suggest that the polymorphic variant of the C589T locus of the IL-4 gene may be associated with RB disease against the background of LHD in children in the Uzbek population.

The cluster of genes encoding the proinflammatory cytokine TNF-α is located on the short arm of chromosome 6 (6p21.1 – 6p21.3) [142].

To date, several functional polymorphic loci have been identified [52,55], among which the most significant is the guanine to adenine substitution variant rs1800629 (G308A).

The frequency of occurrence of the wild G allele of the TNF-α gene in the general sample and control group was statistically insignificant and amounted to 90% and 92.7%.

The unfavorable allele rs1800629 A was rare and was found in 7.3% of the control group and 10% of the main group of patients. Allele A was 1.4 times higher in the main group. When carrying out statistical processing, despite minor differences, a high odds ratio for detecting an unfavorable allele A in patients with RB in the general sample was revealed (OR=1.4; 95% CI: 0.701-2.655, $\chi 2$ =0.8; p=0.4). The relative risk of developing pathology was 1.3 with a confidence interval of 95% CI: 0.721-2.448.

The frequency of the homozygous genotype G/G in the general sample of patients was lower and amounted to 80.7%; in the control group it was 85.5%. The frequency of the G/A genotype in the main group of patients was 19.3%, in the control group it was 14.5%. Indicators of heterozygous carriage of the G/A genotype in the main group of patients tended to increase, which constituted the risk of developing RB (OR=1.4; 95% CI: 0.7-2.83, $\chi 2$ =0.9; p=0.3). The frequency distribution of the unfavorable genotype A/A was not found in any of the groups when analyzed in both study groups.

The unfavorable allele A was statistically significantly more often detected in patients with RB (8.9%) and the relative risk of developing pathology was 1.4 than in children of the control group (7.3%; RR=1.2; 95% CI: 0.585-2.545, $\chi 2$ =0.3; p=0.6), while the wild allele G in children of group I was detected less frequently in 91.1%, compared to 92.7% in conditionally healthy children. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele A in children of the Republic of Belarus increased by 1.2 times, 95% CI 0.557-2.766.

The frequency of the wild homozygous genotype G/G of the TNF-α gene in patients of group I was lower than in conditionally healthy children (82.3%

versus 85.4%, respectively, with RR=1.0; 95% CI: 0.838-1.106, $\chi 2$ =0.4; p=0.6). An increase in the number of homozygotes of the G/G genotype in children of the control group indicates a possible protective effect of this genotype regarding the formation of RB.

The heterozygous genotype G/A among patients of group I was more common compared to controls, and the odds ratio showed that the risk of developing RB in the presence of this genotype increases by 1.2 times (OR=1.3; 95% CI: 0.547-2.935, $\chi 2$ =0.3) .

In patients of group II, statistically more significant differences were revealed in the distribution of frequencies of alleles and genotypes of the polymorphic locus G308A of the TNF-α gene.

The frequency of the wild homozygous genotype G/G of the TNF-α gene in patients of group II was lower than in conditionally healthy children (79% versus 85.4%, respectively, with RR=0.9; 95% CI: 0.791-1.078, $\chi 2$ =1.14; p<0.3). An increase in the number of homozygous G/G genotype in children of the control group indicates a possible protective effect of this genotype regarding the formation of RB against the background of LGD. The heterozygous genotype G/A among patients in group II was more common compared to controls, and the odds ratio showed that the risk of developing RB against the background of LGD in the presence of this genotype increases by 1.4 times (OR=1.6; 95% CI: 0.684-3.588, $\chi 2$ =1.14).The distribution of allele frequencies in patients with RB against the background of LHD showed a statistically significant increase in the unfavorable allele A in patients of group II (10.5%) and the relative risk of developing pathology was 1.4 than in children of the control group (7.3%; RR=1.4; 95% CI: 0.709; 2.954, $\chi 2$ =1.03; p=0.3), while the wild allele G in children of group II was detected less frequently in 89.5%, compared to 92.7% in conditionally healthy children. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele A in children of group II increased by 1.5 times, 95% CI 0.684-3.29.

The frequency of the wild homozygous genotype G/G of the TNF-α gene in patients of group II was lower than in conditionally healthy children (79% versus 85.4%, respectively, with RR=0.9; 95% CI: 0.791-1.078, $\chi 2$ =1.14; p<0.3). An increase in the number of homozygous G/G genotype in children of the control group indicates a possible protective effect of this genotype regarding the formation of RB against the background of LGD. The heterozygous genotype G/A among patients in group II was more common

compared to controls, and the odds ratio showed that the risk of developing RB against the background of LGD in the presence of this genotype increases by 1.4 times (OR=1.6; 95% CI: 0.684-3.588, $\chi 2$ =1.14).

Thus, the results of the study indicate that the G-308A polymorphism of the TNF-α gene affects the level of tumor necrosis factor alpha in the blood of patients with RB on the background of LHD. An unreliable decrease in this cytokine in the remission phase shows that in patients of group II, the acute immune inflammatory process persists longer and can transform into a chronic one.

The gene encoding IL-6 is located on chromosome seven in the 7p21-p14 region, which contains five exons.

The C allele (cytosine) is replaced by the G allele (guanine) in the promoter region of IL-6 C174G. The presence of the G allele is known to cause high levels of circulating IL-6 in the blood of patients [76]. IL-6 stimulates activation of the vascular endothelium, proliferation of smooth muscle cells and induces leukocytes.

The frequency of distribution of alleles C and G of the IL-6 gene in patients with recurrent bronchitis in the general sample was: 77.7% and 22.3%, in the control group 82.3% and 17.7%, respectively.

The observed distribution of allele frequencies for the C174G polymorphism of the IL-6 gene in the groups of patients with RB and the control group revealed statistically insignificant differences (p = 0.2). At the same time, the chance of detecting the G allele was OR=1.3; 95% CI: 0.838–2.10, which allows us to consider this allele as predisposing to the development of RB in children.

Analysis of the distribution of C/C genotypes in the total sample of patients was 62.2%; in the control group, 68.2% was recorded. Indicators of the homozygous genotype C/C decreased compared to the control group (RR=0.9; 95% CI: 0.867-1.820, $\chi 2$ =1.5; p=0.2), being a marker of a low risk of developing RB.

The frequency of heterozygous carriage of the C/G genotype in the total sample of patients was 31.1%; in the control group it was 28.2%. The frequency distribution of heterozygous carriage of the C/G genotype and the mutant G/G genotype did not reveal statistically significant differences (p=0.05

The distribution of alleles C and G of the IL-6 gene in patients with RB was: 79% and 21% and in the control group 82.3% and 17.7%, respectively.

Statistical processing revealed an insignificant increase in the frequency of the unfavorable allele G in patients with RB, while the relative risk of developing pathology was 1.2 times (RR=1.2; 95% CI: 0.758-1.845, $\chi 2$ =0.5; p=0.5).

Analysis of the distribution of C/C genotypes in the group of patients with recurrent bronchitis was 66.1%, in the control group it was 68.2%. Indicators of the homozygous genotype C/C decreased compared to the control group (RR=1.0; 95% CI: 0.546-1.535, $\chi 2$ =0.1; p=0.8). The frequency of heterozygous carriage of the C/G genotype in patients with RB is 25.8%, in the control group 28.2%. Indicators of the heterozygous genotype C/G decreased compared to the control group. (RR=0.9; 95% CI: 0.779-1.208, $\chi 2$ =0.1; p=0.7).

The distribution of frequencies of alleles C and G of the IL-6 gene in the group of patients in group II and control was: 78.1% and 21.9% and in the control group 82.3% and 17.7%, respectively. Statistical processing revealed an insignificant increase in the frequency of the unfavorable allele G in patients of group II, while the relative risk of developing pathology was 1.2 times (RR=1.2; 95% CI: 0.790-1.937, $\chi 2$ =0.86; p=0.4). Analysis of the distribution of C/C genotypes in group II of patients was 57.9%, in the control group 68.2% was recorded. Indicators of the homozygous C/C genotype decreased compared to the control group (RR=0.8; 95% CI: 0.658-1.096, $\chi 2$ =1.74; p=0.2). Indicators of the heterozygous genotype C/G increased compared to the control group. (RR=1.3; 95% CI: 0.832-2.055, $\chi 2$ =1.31; p=0.25).

However, it should be noted that the homozygous G/G genotype increased in patients with RB against the background of LHD, which was 1.4 times higher compared to the control group (RR=1.4; 95% CI: 0.335-6.247, $\chi 2$ =0.25; p=0.6).

Thus, this polymorphism is not a marker of susceptibility to RB against the background of LGD. Although the C allele and the homozygous C/C genotype are protective in the development of the disease.

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ISBN 978-623-464-096-0 (PDF)