DIAGNOSTIC CRITERIA FOR CHRONIC LUNG DISEASES IN CHILDREN

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Annotation.
Bronchopulmonary pathology occupies a significant place in the structure of childhood morbidity. In the last two decades, there has been an increase in the proportion of recurrent and chronic respiratory diseases in children, which often continue into adulthood and are the cause of disability and disability. At the same time, there is an increase in the frequency of severe chronic forms of lung diseases in children, leading to disability already in childhood. The relevance of the problem of inflammatory lung pathology in children is due to the prevalence of the disease, the high mortality rate, and the high economic costs associated with the treatment of patients. The study of scientific literature data made it possible to establish the presence of many links in the protective reaction of the lungs in response to exposure and in various types of pathology. The most significant of them are the genetic mechanisms of development, the state of mucociliary clearance and immune structures, as well as the reaction of endocrinocytes to inflammatory processes in the respiratory system. The formation of these protective structures in the lungs will make it possible to reveal their significance in early postnatal ontogenesis.

Key words: Lungs, chronic lung diseases, children, endocrinocytes.

Introduction

The purpose of our literature review was, based on literature sources, including morphological changes, to study the prevalence and the latest diagnostic criteria for chronic lung diseases in children.

Bronchopulmonary pathology occupies a significant place in the structure of childhood morbidity. In the last two decades, there has been an increase in the proportion of recurrent and chronic respiratory diseases in children, which often continue into adulthood and are the cause of disability and disability [3., 13]. The incidence in children aged 0–14 living in developed countries is considered low and ranges, for example, from 0.5 per 100,000 children in Finland to 3.7 per 100,000 children in New Zealand. However, among Aboriginal children from Central Australia, incidence rates reach 200 per 100,000 children [33]. In India, due to the unsatisfactory level of medical care in children under 4 years of age after pneumonia, bronchiectasis is diagnosed in 212–2646 cases per 1 million children per year [34]. In the Russian Federation, studies on the prevalence of bronchiectasis in children have not been conducted. There is statistical data on the prevalence of nosological forms corresponding to the ICD-10 codes J44 (other chronic obstructive pulmonary disease) and J47 (bronchiectasis disease), children from 0 to 14 years old: 98.3 per 100,000 in 2010 and 89.3 per 100,000 child population in 2011 [19]. Thus, bronchiectasis remains an important problem affecting socially disadvantaged groups, especially children living in developing countries where there is overcrowding, poor hygiene, and limited access to medical care. Mortality from respiratory diseases in the vast majority of cases are young and middle-aged people, as well as children and adolescents, it becomes obvious the relevance of the problem of early diagnosis and treatment of these patients [4].

Materials and methods

Respiratory diseases are the most common childhood pathology. Pulmonary diseases account for one in six deaths worldwide. Currently, the problem of prevention and treatment of bronchopulmonary diseases in children remains relevant. In the structure of primary morbidity, this pathology occupies one of the first places in children of all age groups. These diseases are fraught with various complications. They can take a chronic form with exacerbations, are involved in the occurrence and progression of lung diseases, and also affect the immune system [15., 25., 26]. At the same time, there is an increase in the frequency of severe chronic forms of lung diseases in children, leading to disability already in childhood [2]. Chronic bronchitis is a common form of chronic non-specific disease of the bronchopulmonary system, the resolution of the XIV Congress of Pediatricians of Russia with international participation emphasizes that among children of all ages there is a predominant increase in chronic

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pathology. Its share in the structure of all health disorders currently exceeds 30% [42]. It was revealed that the development of chronic bronchitis is facilitated by frequent acute respiratory diseases, chronic inflammatory and suppurative processes in the lungs and upper respiratory tract, a decrease in the body's reactivity, and excessive secretion of mucus in the bronchial tree. [13.]. The development of obstructive forms of acute bronchitis in young children is associated with impaired cellular humoral immunity. An important place in this process is occupied by neutrophilic leukocytes. Depending on the period of the disease, they can quickly rebuild their metabolism, carry out adhesion, degranulation, migration, phagocytosis, and endocytosis, activation of several humoral systems of the body. In bronchopulmonary pathologies, neutrophilic leukocytes affect the development, course, and outcome of the disease. Kautsky et al. and others in their studies have found a decrease in the immune system in children who are frequently ill and children with allergic diseases. [7] A lot of scientific literature is devoted to the issue of COPD etiology, the main conclusions of which are that the origins of the disease are processes that lead to bronchial deformation and pneumosclerosis. [19.,26]. Sosyura V.Kh. (2007) in their studies cite the facts of the development of chronic lung diseases, segmental and lobar atelectasis [13]. A violation of the drainage function of the bronchi leads to the chronic course of the pulmonary process in the bronchi and lungs, which contributes to the emergence of an infectious process, the activity, and relapses of which largely depend on the local immunity of the bronchi and the development of secondary immunological deficiency [10., 22]. It has been proven that often chronic inflammatory diseases of the bronchopulmonary system are complicated by obstructive syndrome [8., 14., 20]. The outcome of a chronic inflammatory process in the bronchi is sclerosis of the bronchial wall, peribronchial sclerosis, atrophy of the glands, muscles, elastic fibers, and cartilage of the bronchi, and the formation bronchiectasis. In recent years, the role of nitric oxide and interleukins in chronic bronchopulmonary pathology in children has been actively studied [12]. Several works over the past 10-15 years have been devoted to the study of the spread and various clinical forms of chronic bronchitis. In the literature, there is evidence that chronic bronchitis in children can be a manifestation of several other bronchopulmonary sufferings [3]. Thus, summing up the above, we can say that COPD remains a common disease, and the number of patients continues to increase, this is most likely due to the difficulties in detecting pathology due to the blurring of clinical manifestations, the frivolous attitude of this contingent to mild symptoms of the disease.

According to many authors, the diagnosis of chronic lung diseases should be based on a combination of anamnestic data and characteristic clinical, laboratory, radiological, functional, fluorographic, and conchological methods: bronchoscopy and bronchography, the technique and technology of which are continuously being improved. [11., 13., 28., thirty]. Note that, according to Zgherea D. et al. (2012) et al. (2012) et al., the study of the bronchial system using high-resolution X-ray computed tomography is comparable to bronchography, especially in the diagnosis of bronchiectasis [65.]. High-resolution X-ray computed tomography normally visualizes bronchioles up to 2-3 mm in diameter. This allows you to recognize the pathology of the lungs in the early stages of development. Literature sources note that the study of the characteristics of bronchial contents is a reliable method of intravital morphological diagnostics, which makes it possible to establish the etiology, type, and activity of the inflammatory process, the state of local pulmonary protection, and to judge the need and effectiveness of sanitation of the bronchopulmonary system [23].

The study of bronchial lavage makes it possible to describe morphological changes in the bronchi, however, these studies in pediatric practice were carried out in isolated cases.

In recent years, it has been accepted that bronchiectasis is a multietiological pathology, the pathogenesis of which involves a complex interaction between the body, respiratory pathogens, and environmental factors. This interaction leads to a vicious cycle of recurrent infections, inflammation of the airways, and tissue remodeling contributes to impaired clearance, destruction of the structural elements of the bronchial wall forms dilatation, and obstruction of the small bronchi. The literature emphasizes the central role of neutrophils in the pathogenesis of bronchiectasis. Proteases formed in the lungs as a result of the inflammatory response damage the airways and lead to pathological dilatation, which is the pathognomonic sign of bronchiectasis. Small airways show infiltration of lymphoid follicles, which may contribute to local obstruction of small airways. Despite aggressive treatment, the disease persists in most patients. Manipulating the immune response in bronchiectasis could potentially have the therapeutic potential [49].

Among children, bronchiectasis occupies an important place in the structure of bronchopulmonary pathology. In this regard, attention to the study of various aspects of this disease, including its etiopathogenesis, continues unabated. Recent genetic, structural, and functional studies have revealed that the mucosal epithelium of the respiratory tract and lungs is a key organizer of the immune response. In addition, there is now strong evidence that epithelial dysfunction is involved in the development of inflammatory lung diseases [33, 34, 55, 57]. The basis of the formation of bronchiectasis can be congenital and hereditary diseases. Congenital anomalies in the development of the bronchopulmonary system are detected in 8-10% of patients with chronic inflammatory lung

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diseases [17.,18.,51.,52]. It was found that only 18.0% of patients had congenital bronchiectasis. At the same time, it turned out that 38.5% of children had a hereditary predisposition to respiratory diseases [16]. There is evidence that chronic pulmonary suppuration subject to surgical treatment in 66% of children is due to congenital malformations of the lungs. However, according to several researchers, even with a carefully conducted differential diagnosis in 26-53% of cases, the cause of the formation of bronchiectasis cannot be established [6., 16.,33.,36.,45.,48].

Results

Bronchiectasis is divided into cylindrical, saccular, and mixed. In addition, fusiform, cystic, and varicose bronchiectasis have been described. Because different variants of bronchiectasis can occur in one patient, the localization and prevalence of changes within specific bronchopulmonary segments are of the greatest importance. Cylindrical bronchiectasis, as a rule, occurs with sclerosis of the bronchial walls.

. At the same time, the lumen of the bronchus evenly expands over a sufficiently large extent. Often this occurs against the background of other lung diseases - secondary bronchiectasis. The cylindrical shape of bronchiectasis does not contribute to the accumulation of a large volume of pus, so the general condition of the patient, as a rule, is not too severe, and sometimes such bronchiectasis can regress when the cause that caused them is eliminated (infection, atelectasis, aspiration by a foreign body) [56,59]. Saccular bronchiectasis - single spherical or oval expansions on one side of the bronchus. Quite often, this form of bronchiectasis occurs with congenital defects in the development of bronchopulmonary tissue. Bags are blind protrusions of the wall, which can reach large sizes. Characterized by the accumulation of a large amount of sputum and pus. The course of the disease is usually severe [5., 9., 28., 31., 32., 53., 57.].

Despite numerous scientific studies devoted to the study of patterns of mortality in inflammatory pathologies, the role of immuno-endocrine relationships between lung structures in inflammatory pathologies and diagnostic criteria have not been fully defined. An important task is to introduce into clinical practice the algorithm of complex diagnostics, prognostic criteria, and evaluation of the outcomes of criteria for diagnosing immuno-endocrine relationships of lung structures in inflammatory pathology in children. The components of the APUD system are called neuroendocrine, as they are expressed by genes of both neuronal and endocrine cell phenotypes, including the synthesis and release of amine (serotonin, 5-HT) and various neuropeptides (including bombesin). Hyperplasia of podocytes and NET has been established in chronic diseases in children, as well as in experimental pneumonia. In recent years, intensive studies of neuroendocrine cells of the lung APUD system have been carried out in many physiological and pathological conditions of the organ [25., 26]. Biologically active substances and regulatory neuropeptides secreted by respiratory podocytes (neuroendocrine cells) into the lumen of the respiratory tract affect all mechanisms of formation and development of bronchial obstruction, remodeling of the airways, and respiratory system [18]. It was possible to identify a relationship between age-related features of bronchial mucosa lesions, impaired pulmonary microcirculation, changes in bronchial patency, the development of pulmonary emphysema, and the nature of podocyte activity, as well as the content of amines in the bronchial mucosa in patients with atopic bronchial asthma. So, in their opinion, the high activity of respiratory podocytes somehow prevents the development of emphysema in patients with bronchial asthma, causes a mild course of the disease, and the absence of pronounced atrophic changes in the bronchial mucosa. The probable cause of the changes, the authors believe, is the secretion by these cells of certain, perhaps still unknown, biologically active substances and regulatory neuropeptides [17., 52].

The genetic mechanisms of the development of chronic bronchitis in children have been little studied. The genetic mechanisms of the formation of acute and chronic respiratory diseases have become the object of large-scale research throughout the world in recent years [29.,38.,39.,40]. An integral part of preventive programs today is genetic screening. The implementation of hereditary predisposition to CB is associated with genetically determined structural and functional features of metabolism, neurohumoral regulation, and local factors. In their epidemiological or clinical studies, foreign scientists note the participation of genetic factors in the occurrence of CB, which suggests the existence of specific genes responsible for the occurrence of this disease. The molecular genetic method for predicting the formation of CP makes it possible to identify a predisposition to the disease at any age, practically from the birth of a person, since the genotype of a particular individual does not change throughout life. In addition, predisposition to the disease can be established using this method in the absence of any clinical, biochemical or immunological manifestations, i.e., at the earliest preclinical stage in the development of pathology. The sooner the presence of a genetic marker is detected, the more reliable and timely the measures to prevent the disease will be. Reducing the incidence of chronic bronchitis due to early effective detection of predisposition to it, as well as more effective prevention of chronic bronchitis, will lead to a significant reduction in material costs for the organization and implementation of therapeutic measures. It is known that the leading role in the process of destruction of the alveolar matrix belongs to pro-inflammatory cellular proteinases [41.,46]. Proteolytic enzymes are the main regulators of inflammatory and immune reactions associated not only with the degradation of extracellular

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matrix proteins and the release of bound interleukins, but also with cleavage of cytokines and chemokines, and, as a result, modulation of the biological activity of inflammatory mediators. Among them are matrix metalloproteinases (MMPs, Matrix Metalloproteinases), a family of 26 enzymes that are an integral part of the processes of development, tissue remodeling, and recovery. Pathological MMP expression is associated with many destructive processes, including tumor tissue proliferation, arthritis, arterial aneurysms, and pulmonary emphysema [38]. Conducting a molecular genetic study can reduce the incidence of CB in children by identifying a predisposition to its development [40.,41]. At the same time, the identification of gene polymorphism with the manifestation of chronic bronchitis in children can contribute to the solution of the problems of forming risk groups and the implementation of preventive measures among these groups, as well as a better understanding of the pathogenesis of this condition. In this regard, the question of what is the quantitative contribution of genetic mechanisms in the development of the leading symptoms of CB in children is very relevant. The results of genome-wide linkage analysis in chronic respiratory diseases showed a high degree of linkage of loci on chromosome 19q - tag-beta1 (transforming growth factor beta 1, transforming growth factor beta1) and chromosome 2q - serpIne2 (serpin peptidase inhibitor, clade e, serpin peptidase inhibitor type) [59]. Genome-wide studies of genetic associations (GWAS) revealed several loci associated with the development of 23 chronic respiratory diseases: on the 4th and 15th chromosomes in the 15q25.1 region - Chrna3, Chrna5 (cholinergic receptor nicotinic alpha 3, cholinergic nicotinic receptors alpha 3 and 5), IREB2 (iron responsive element binding protein 2, iron-binding element protein 2), PSMA4 (proteasome subunit alpha type 4, subunit alpha type 4 of the proteasome complex), 4q31.21 –HHIP (hedgehog interacting protein, interacting hedgehog signaling pathway protein), 4q22. I - F AMI 3A (family with sequence similarity 13 member A, family member A with similar sequence 13) and a new marker rs7937 on chromosome 19qL3 [64.]. Before the “GWAS Era”, the genetic component of chronic obstructive pulmonary diseases was actively studied using the analysis of candidate genes [42.,64]. This method is still the most widely used in research on the genetics of chronic lung diseases since it allows focusing on one or more functionally significant allelic variants of a gene encoding, respectively, protein variants that differ in structure and function, some of which may be involved in the development of pathogenetic diseases. changes [60.,63].

Despite a significant number of studies performed using different approaches, the molecular genetic basis of chronic respiratory diseases is still largely unclear [41.,42]. Working in various directions will make it possible to get closer to understanding the complex processes leading to the development of the disease [56.,59]. It is known that the greatest role in the process of destruction of the alveolar matrix belongs to pro-inflammatory cellular proteinases [60.,61]. Matrix metalloproteinases (maps, matrix metalloproteinases) are a family of 26 enzymes that are an integral part of 24 processes of development, tissue remodeling, and repair [59.,60.,64]. Pathological MMP expression is associated with many destructive processes, including proliferation. The chronic bronchopulmonary diseases selected for this study in children occupy a leading position in terms of prevalence, severity, and severity of complications and are the main causes of high rates of morbidity, disability, and mortality, which indicates the relevance of studying the genetic basis of these diseases and finding out the main causes of their occurrence. [64].

Candidate genes involved in the development of CP in children include genes such as IRF-4 and MMP12, IL-10, and SCGB1A1. Interleukin-10 is a pleiotropic cytokine that plays an important role in the regulation of immune processes. Severe forms of the infectious process are accompanied by hyperproduction of pro-inflammatory cytokines with the formation of an extended inflammatory response [35., 38., 44., 47]. In this regard, there is a need to determine an in-depth study of the clinical and pathogenetic mechanisms of chronic bronchitis in children, the study of genetic polymorphisms, the development of criteria for their diagnosis, which is essential for early recognition of the disease and the selection of adequate therapeutic measures aimed at preventing the progression of the process. Predominantly neutrophilic inflammation in COPD causes partially reversible bronchial obstruction, which steadily progresses even against the background of modern therapy, and predominantly eosinophilic inflammation in asthma causes completely or almost completely reversible bronchial obstruction, which can be resolved even in the absence of treatment. Together, However, the intensity of inflammation, as well as its cellular and molecular characteristics, change during the progression of these diseases [21., 22].

Both small airway remodeling and emphysema are likely the results of chronic inflammation. Chronic lung inflammation in stable COPD is characterized by infiltration of neutrophils, monocytes, cytotoxic CD8∟ and CD4∟ Th1 and Th17 T-lymphocytes. Cell recruitment is initially triggered by chemotactic signals elicited in macrophages and epithelial cells by smoke and air pollutants through oxidative stress and mediated by toll-like receptors [55]. Airway mucosal metaplasia and chronic inflammation are pathophysiological features that influence morbidity and mortality associated with asthma and other chronic lung diseases. Elucidation of the molecular mechanisms regulating mucosal metaplasia and hypersecretion provides the scientific basis for diagnostic and therapeutic options to improve the management of chronic lung disease [44].

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In the subgroup of COPD patients with a predicted FEV1 of 80%, there is an inverse relationship between goblet cell metaplasia detected histopathologically in surgical specimens and preoperative FEV1. Thus, patients with higher FEV1 have less goblet cell metaplasia than those with lower FEV1, suggesting that the presence of mucin-producing cells in the airways is associated with increased airflow obstruction. The progression of COPD is closely associated with the accumulation of inflammatory mucosal exudate in the lumen of the small airways, and the presence of a pronounced goblet cell phenotype is negatively correlated with the change in FEV1 after lung volume reduction surgery. Taken together, these results indicate that mucus in the airway lumen can be significant enough to lead to measurable mechanical obstruction of the small airways, and this can significantly affect the pathogenesis and prognosis of the disease [45, 49, 64]. Hypersecretion of the mucosa causes a chronic productive cough. This is characteristic of chronic bronchitis, but not necessarily. associated with airflow obstruction, and not all patients with COPD have symptomatic mucosal hypersecretion. The hypersecretion is associated with squamous metaplasia, increased number of goblet cells, and increased size of bronchial submucosal glands in response to chronic irritation by noxious particles and gases. Ciliary dysfunction occurs due to squamous metaplasia of epithelial cells and leads to an abnormal mucociliary escalator and difficulty in expectoration [27., 32., 45., 64].

Chronic lung inflammation in stable COPD is characterized by infiltration of neutrophils, monocytes, cytotoxic CD8∟ and CD4∟ Th1 and Th17 T-lymphocytes. Cell recruitment is initially triggered by chemotactic signals induced in macrophages and epithelial cells by smoke and air pollutants through oxidative stress and mediated by toll-like receptors [54]. In addition, at present, the immunohistochemical method (IHCM) is widely used in pathological and anatomical diagnostics. Differential diagnosis of tumors using IHCM is based on the fundamental features of tumor growth, which include the preservation of the expression of functioning genes under conditions of malignant cell transformation. The immunohistochemical method is also used to diagnose several rare lung diseases (in particular, Langerhans cell histiocytosis), lung lesions in lymphogranulomatosis, and other lymphoproliferative diseases. The use of the CD1a marker makes it possible to confirm the presence of Langerhans cells in the granuloma in histiocytosis. Detection of Hodgkin's cells, as well as CD15 and CD30-positive cells (Berezovsky-Sternberg cells) in the infiltrate, allows confirming the diagnosis of lymphogranulomatosis. Immunophenotyping in lymphomas with lung involvement allows for determining the cellular variant and prognosis of the disease. The immunohistochemical method in several inflammatory diseases allows us to clarify the nature of the immunological process, depending on the participation of various subpopulations of lymphocytes in it. In some cases, IHCM makes it possible to differentiate the inflammatory infiltrate from the tumor process [22]. Subsequent in vivo quantification of HB-EGF protein expression by Western blotting confirmed that the protein is highly expressed 6-24 hours after bacterial inoculation, while immunohistochemistry revealed production by middle ear epithelial cells and infiltrating lymphocytes. The data obtained indicate the active role of HB-EGF in the hyperplasia of the epithelium of the mucous membrane of the middle ear in otitis media. These results suggest that HB-EGF-targeted therapy may improve mucosal growth during otitis media and, how reduce the harmful effects of this childhood disease. [62.,63]. New porcine cystic fibrosis (CF) models are expected to mimic human disease more accurately than existing mouse models. However, little is known about the tissue and cellular expression patterns of the porcine CF transmembrane conductance regulator (CFTR) and possible differences from human CFTR (CFTR). Here, the expression pattern of pCFTR has been systematically established at the mRNA and protein levels. Using specific antibodies against pCFTR, most of the protein was immunohistochemically detected on paraffin-embedded and cryostat sections in the apical cytosol of intestinal crypt epithelial cells, nasal, tracheal, and bronchial epithelial cells, as well as other selected, mainly glandular, epithelial cells [51]. Serous cells also play an important role in innate airway immunity by secreting lysozyme, lactoferrin. The serous cells of the submucosal glands have been hypothesized to play a particularly important role in the pathology of cystic fibrosis. This disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane anion channel expressed in various epithelia, including the respiratory tract [63].

In cystic fibrosis, dehydrated and acidic ASL impairs critical innate defense mechanisms, including mucociliary clearance. There are currently discussions about airway cell types that express CFTR, but it is found in the submucosal airways and some surface epithelial cells, including multiresistant cells (low expression) and recently, described lung monocytes (high expression). Whether cellular autonomic loss of CFTR is itself hyperinflammatory is debated, but the combination of mucus stasis and chronic infection leads to severe airway inflammation in CF. The complex interactions during infection arising from the defect in the epithelium eventually lead to pathological changes, including extensive mucus obstruction, ectasia of the bronchi and bronchioles, and consequent loss of lung function. Significant structural damage to the airways and surrounding parenchyma will likely become irreversible, and the goal of airway epithelial cell therapy is to intervene at an early stage, probably in childhood [24,26]. The SAM-sharp domain containing Ets-like factor (SPDEF) plays a critical role in the regulation of the transcriptional network mediating goblet cell differentiation and mucus hyperproduction associated with

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chronic lung disease. [66.,67]. The results suggest the potential utility of AAV pseudotyped vectors for the treatment of cystic fibrosis. The human fetal tracheal xenograft model can serve as an effective tool to further develop fetal gene therapy strategies for the intrauterine treatment of cystic fibrosis. [41., 43].

In recent years, there has been great interest and research in stem cells with the hope of using such cells in tissue regeneration. Stem cells are a heterogeneous group with different possibilities of self-renewal and differentiation [17]. Diffuse lung ossification (DPO) is a rare disease characterized by bone formation in the lungs. DPO can be divided into idiopathic lung ossification (IPO) and secondary lung ossification. Cases with no established etiology are classified as IPOs. Disheveled associated activator morphogenesis 2 (DAAM2) variants are reported to be involved in bone resorption of osteoclasts. [61].

In any inflammation, inflammatory cytokinins are produced. Repeated respiratory diseases in early childhood activate clones of type 2 T helpers (T112) and inhibit type 1 helpers, with suppression of the suppressor activity of T-lymphocytes. Recurrence of diseases contributes to an increase in the production of Il-4 by lymphocytes, and hyperproduction of IgE [56., 65., 66.]. Deficiency of the humoral link of immunity in the form of a decrease in serum IgA, the amount of which correlates in serum and secretions, contributes to the disruption of the interaction of macrophages and lymphocytes during infections in the respiratory system [37]. A feature of the functional morphology of the immune system is excessive dynamism. In its organs, the processes of proliferation, differentiation, migration, cooperation, and apoptosis of lymphocytes are constantly going on. The circadian organization of the immune system was revealed, and the dependence of the morphofunctional state of the immune system on the structure of its daily organization was shown [15].

According to modern concepts, atopic bronchial asthma is a disease accompanied by chronic inflammation of the bronchi, causing recurring episodes of bronchial obstruction and hyperreactivity of the airways. A certain degree of activity of cells entering the state of apoptosis corresponds to the severity of the course of the disease and affects the progression of the inflammatory process in the bronchus pulmonary system in atopic bronchial asthma. At the same time, traditional pathogenetic therapy of bronchial asthma leads to a significant change in the level of CD95+- lymphocytes in circulating blood [1].

It has been established that in COPD and CB there is a significant imbalance of cytokines in the blood serum of patients: increased levels of pro-inflammatory cytokines IL-1β, TNF-a, IL-6, IL-8; the level of IL-2, IFN-γ is reduced, dynamic changes in the content of anti-inflammatory cytokines are observed. Determination of serum concentrations of IL-2 and IFN-γ should be used as a marker of the severity of COPD and immune deficiency. Immune disorders in COPD dictate the need to prescribe complex therapy with the inclusion of immunoprotective drugs, the action of which is aimed not only at suppressing inflammation but also at restoring the impaired immunity link, the altered balance of cytokines. Immunotherapy is indicated for patients with an imbalance of cytokines as part of complex treatment [58]. In people with COPD, IL33 gene expression has also been associated with IL-13 and mucin gene expression, and IL33 induction has been traced to a subset of airway basal cells with increased pluripotency and ATP-regulated release of IL-33. Together, these findings provide a paradigm for the role of the innate immune system in chronic disease based on the influence of long-term epithelial progenitor cells programmed to overproduce IL-33. [27].

Functional studies using live cell fluorescence to measure intracellular pH showed that IL-17A induced chloride-bicarbonate metabolism in HBE cells, which was not present in the absence of IL-17A. In addition, HBE cells treated with anti-pendrin short interfering RNA showed a significantly reduced chloride-bicarbonate exchange. These data suggest that pendrin is part of IL-17A-dependent epithelial changes and that pendrin may therefore be a therapeutic target in IL-17A-dependent lung disease [24]. The effect of H2S synthesis inhibitors of H2S donors on the severity of esophagitis, as well as changes in serum levels of pro-and anti-inflammatory cytokines (IL-17 and IL-10, respectively) was investigated. Exposure to water-immersion stress after drinking fructose-supplemented water for 28 days resulted in esophageal submucosal edema and neutrophil infiltration, as well as muscle plate lesions and basal cell hyperplasia. Suppression of H2S synthesis led to a significant exacerbation of inflammation and injury. Serum IL-17 levels were significantly elevated, while serum IL-10 levels were decreased [67]. A significant place in the structure of the waiting list also belongs to recipients for whom diabetes has become the reason for the loss of kidney function, including type I diabetes, which is also an autoimmune disease. At the same time, it is known that HLA-DRB1 homozygosity is one of the factors that determine a high level of predisposition to the development of this autoimmune disease [14.,17]. Patients with COPD+EP have a higher intensity of respiratory symptoms, comorbidity index, and blood C-reactive protein levels, lower spirometric parameters compared to patients with exacerbation of COPD. The course of the disease both in patients with COPD + CAP and in patients with exacerbation of COPD is accompanied by immunological disorders. In patients with COPD + CAP, compared with patients with COPD, T-helper, and T-suppressor cell activity are reduced, and the level of B-lymphocytes, IgM, IL-6, and TNF-α is increased. After treatment, in patients with COPD+EP, clinical symptoms and manifestations of

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systemic inflammation remained more pronounced, the content of NK cells and IgG remained low, and the levels of CD19+ lymphocytes, IgM, and pro-inflammatory cytokines remained high [15]. IL-13-induced goblet cell metaplasia in human airway epithelium is long-lasting but reversible. Mucus hypersecretion can persist for years, even after the initial trigger (eg, quitting smoking) has been removed (39–41). Because mucus hypersecretion in high Th2 asthma can be reduced by blockade of the Th2 pathway (52), we hypothesized that removal of IL-13 might alleviate IL-13-induced goblet cell metaplasia [50].

Summarizing the review of the literature, it can be stated that insufficient dispensary work and a low level of diagnosing a particular pulmonary disease lead to the fact that children are treated with other diagnoses, inadequately. As a result, the majority of children arrive with a neglected pathological process, which is almost amenable to conservative therapy and requires surgical interventions, for example, bronchiectasis. Analysis of the literature showed that, despite the progress made in the study, diagnosis, and treatment of nonspecific lung diseases in children, there are several unresolved scientific problems.

x and practical problems: - the importance of bronchial patency, insolvency of local pulmonary protection and adverse features of the inflammatory reaction of the respiratory sections of the lungs at the stages of the formation of nonspecific lung diseases have not been sufficiently established.

A diagnostic program has not been developed to reliably determine the safety of the respiratory structures of the lung, the nature of the inflammatory reaction, and the recognition of congenital malformations of the bronchopulmonary system in children. The system of staged therapeutic and preventive measures when using a complex of therapeutic, endoscopic methods is not justified. The methods of endoscopic correction of violations of bronchial patency and the associated insufficiency of local pulmonary protection require further improvement and pathogenetic substantiation. Active detection of chronic bronchitis in children at the early stages of their formation and development of criteria for timely diagnosis and prevention measures by studying the association of polymorphic genetic markers of the IRF-4 and MMP12 genes in children with chronic bronchitis is timely and relevant.

Conclusion

The relevance of the problem of inflammatory lung pathology in children is due to the prevalence of the disease, the high mortality rate, and the high economic costs associated with the treatment of patients. However, timely diagnosis of these diseases is often difficult, since clinical symptoms usually appear with the addition of an infection and the subsequent development of chronic inflammation in the bronchi. There is no information in the literature about structural changes and differential diagnostic criteria based on immuno-morphofunctional conditions in inflammatory lung pathology in children. There is a fairly large number of studies devoted to the morphological characteristics of the branches of the lungs in various diseases. However, they are more often descriptive; there are single works devoted to immunological studies of the endothelium and muscular membrane of blood vessels and elastic membranes. Morphometric studies are fragmented and contradictory. The morphometric characteristics of blood vessels and elements of the immune and endocrine systems of the lungs in various forms of pathologies have not been sufficiently studied. Publications on the presence or absence of congenital and acquired defects with varying degrees of respiratory pathology are contradictory.

However, structural features of endocrinocytes and their relationship with the components of the lung immune system in children with bronchiectasis have not been studied so far. In this regard, it is not possible to fully assess the morphofunctional state of the relationship of the immunoendocrine apparatus of the lungs in inflammatory pathological processes, including bronchiectasis. The genetic mechanisms of the development of COPD in children are not well understood.

Thus, the study of scientific literature data made it possible to establish the presence of many links in the protective reaction of the lungs in response to exposure and various types of pathology. The most significant of them is the genetic mechanisms of development, the state of mucociliary clearance and immune structures, as well as the reaction of endocrinocytes to inflammatory processes in the respiratory system. The formation of these protective structures in the lungs will make it possible to reveal their significance in early postnatal ontogenesis.

Summarizing the literature data on the diagnostic approaches of chronic nonspecific lung diseases in children, it can be noted that anamnestic data, as well as clinical, radiological, conchological, pathomorphological studies, and others, are of paramount importance for the diagnosis of these diseases. The information obtained can be used for the prevention and treatment of lung diseases in children.

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