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CLINICAL, LABORATORY, AND GENETIC INDICATORS OF MUCOVICIDOSIS IN CHILDREN

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Abstract
The article presents an analysis of the results of clinical and laboratory studies. In children with cystic fibrosis, the main clinical symptoms from the bronchopulmonary system were: cough, shortness of breath, oral wheezing, lethargy and loss of appetite. Upon admission to the hospital, the general condition of the patients was most of all regarded as severe. The most common pathogens of exacerbation of the disease were S. aureus – 31 (26.0%) Pseudomonas aeruginosa - 24 (20.0%). Based on the results of the study, the frequency of mutations in the CFTR gene and their effect on the nature of the course were determined. The significant role of the 4 mutations of the CFTR-F508del, CFTR-2143delT, R709X, Y569D gene, which are most common in Uzbekistan, has been revealed.

Keywords: cystic fibrosis, mutation, microbiology, children.

Резюме
В статье представлены анализ результатов клинических и лабораторных исследований. У детей с муковисцидозом основными клиническими симптомами со стороны бронхолегочной системы были: кашель, одышка, пероральные хрипы, вялость и потеря аппетита. При поступлении в стационар общее состояние больных больше всего расценивалось как тяжелое. Наиболее часто встречающимися возбудителями обострения заболевания были S. aureus – 31 (26,0%) Pseudomonas aeruginosa - 24 (20,0%). На основании результатов исследования определена частота мутаций в гене CFTR и их влияние на характер течения. Выявлена достоверная роль наиболее часто встречающихся в Узбекистане 4 мутации гена CFTR-F508del, CFTR-2143delT, R709X, Y569D.

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Ключевые слова: муковисцидоз, мутация, микробиология, дети.

Introduction

Relevance

The relevance of the problem of cystic fibrosis is that the disease requires early diagnosis, constant treatment with expensive drugs, active dispensary observation, accompanied by a low life expectancy of patients and always leads to early disability of patients [2]. Recently, cystic fibrosis has been one of the leading hereditary diseases in children.

Mucoviscidiosis (MV) or pancreatic cyst fibrosis, the most common in the world, is a serious monogenic human disease caused by mutations in the transmembrane protein regulator gene (CFTR), characterized by damage to all exocrine glands of vital organs and systems, usually with a severe course and prognosis [1]. Disruption of CFTR work leads to the formation of a dense, dehydrated secretion in several organ systems, however, changes in the bronchopulmonary system have the greatest impact on the course of the disease and are the main cause of death [4,7].

The cause of MV is mutations in a gene that is referred to as a transmembrane conductance regulator (CFTR - cystic fibrosis transmembrane conductance regulator). The CFTR gene controls secretory processes through mechanisms that have not yet been sufficiently studied. The secretions of the exocrine glands become dense, leading to the development of a multi-system disease (with the involvement of the bronchopulmonary system, digestive system, primarily the pancreas of the daughter gland and liver, the reproductive system) and, as a result, premature death [3]. The basis for the diagnosis of cystic fibrosis is typically the typical clinical manifestations of the disease in combination with a high content of sodium chloride in the secretion of the sweat glands [5].

The lifespan of such patients is closely related, first of all, to the preservation of respiratory function, which seriously suffers due to mucociliary clearance disorders, leading to the development of the disease

severe chronic respiratory infections from an early age and progressive respiratory failure [8]. The functional state of the bronchopulmonary system plays a leading role in the prognosis of the disease. In cystic fibrosis, the local defense mechanisms against the background of respiratory viral infections, which "open the gates" for the penetration of pathogenic microorganisms - Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa and others, are especially severely weakened. Most often, the first bacterial agent that affects the lower respiratory tract is S. aureus (it is most often sown from the sputum of children with MV in the first year of life). Later, P. aeruginosa appears as part of the pathogenic microflora. It can be confidently said that the child's lower respiratory tract is chronically colonized by these microorganisms.

Mucoviscidosis is more common in infancy. Despite the polymorphism of clinical manifestations, a triad of syndromes is typical: respiratory, intestinal (with typical stool) and dystrophic (by type of hypotrophy). As a result of severe chronic hypoxia, there is often deformity of the fingers of the hands ("drum sticks") and fingernails ("clockwork"). Obstructive syndrome, a coccal-like cough are common. The liver and spleen are enlarged, and the rectum is falling out. The stool in patients with cystic fibrosis is liquid, abundant, frequent, and odorous. The coprogram expresses steatoresis, creatoresis, and very low activity of tripsin foal [5]. Our research examined the

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comprehensive assessment of clinical and laboratory studies in children with cystic fibrosis in Uzbekistan.

The purpose of the study

To study the clinical manifestations and laboratory features of cystic fibrosis in children.

Materials and research methods

We examined 120 patients aged 0 months to 14 years who were hospitalized at the Pulmonology, Early Childhood Pathology and Gastroenterology Department of the Republican Scientific and Practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan, of whom the diagnosis of cystic fibrosis was confirmed by clinical examination. These children also had a positive response to cystic fibrosis using the immunoreactive trypsin method.

Bacteriological material for the study was sputum, deep smears from the posterior wall of the throat, bronchial secretion during bronchoscopy. The processing of the data included the results of sowing with a diagnostically significant titer (more than 106 colony-forming units).

The presence of rare CFTR variants was analyzed by mass-parallel sequencing of the entire CFTR encoding region and neighboring introns in combination with CFTR rearrangement analysis.

Results and their discussion

An in-depth clinical and laboratory examination of patients with cystic fibrosis was conducted. Among the children we observed, girls predominated. In the study of children's life history, the first symptoms of the disease from the respiratory system were persistent coughing, which transitioned into a convulsive cough with difficult to separate viscous sputum in all patients. Mixed breathing was observed in 19.2% of children.

Timely hospitalization and medical care have a significant impact on the course and outcome of cystic fibrosis. The observed children were admitted for treatment and examination at different times from the onset of the disease. Thus, in 16 (13.3%) cases, children were admitted to the hospital on the 3-5th day, 40 (33.3%) - on the 5-7th day, and 64 (53.3%) patients were admitted to the hospital for 8 or more days after unsuccessful treatment at home.

The patients' general condition on the day of admission was assessed as very severe in 24 (20%), severe in 64 (53.3%), and moderate in 32 (26.7%) children.

All observed patients underwent a thorough analysis of their life history. Analysis results showed that most patients with cystic fibrosis were born from II-III pregnancies - 58 (49%) and I - 45 (37.5%) pregnancies, and from IV and more pregnancies - 17 (14.2%) children.

Adverse premorbid background significantly affects the severity of the disease in children. Analyzing the background conditions of the patients, we found that 112 (93.3%) children had grade I-II anemia, 60% had allergic diathesis, 53.3% had residual rachitis, and 73.3% had hypotrophy. In children with cystic fibrosis, background complications are already a co-morbidity, significantly aggravating the course of the main pathology.

On admission to the hospital, the main complaints of the parents of the sick children were convulsive 107 (89.2%) cough, first dry, fatty stool 97 (81%), strangulation attacks 18 (15%),

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mixed breathing 54 (45%), loss of appetite 67 (56%), weakness 54 (45%), pallor 112 (93%), sleep disturbance 51 (42,5%), constipation 38 (32%).

Among 56 patients with MB, chronic bronchitis was found in 30 (53.6%),

recurrent obstructive bronchitis was observed in 18 (32.5%), acute and recurrent pneumonia in 29 (51.8%), bronchiectasis in 6 (11.6%), pulmonary blisters in 1 (1.7%), rectal mucus loss in 1 (1.7%), physical development delay in 30 (53.6%), and chronic pancreatic insufficiency in 39 (71.3%).

Bronchopulmonary changes in children play a decisive role in the clinical picture of cystic fibrosis and in 90% of cases determine the course and prognosis of the disease. This is due to the development of mucociliary insufficiency, impaired function of the ciliated epithelium of the bronchial mucosa. Therefore, excessively viscous sputum lodges in the respiratory tract, primarily in the small bronchi and bronchioles, mucosas develops, then bacterial flora joins and inflammatory process begins.

Among the 92 patients with MB we examined, diagnostic titers in the bronchial secretion during bacteriological examination of the nasal swab revealed that 31 (26.0%) cases were dominated by staphylococcus. Aureus, with 24 (20.0%) Pseudomonas aeruginosa.

For the first time in Uzbekistan, we studied more than 3,000 frequent mutations of the CFTR gene associated with cystic fibrosis, of which 4 significant markers were identified: CFTR-F508del, CFTR -2143delt, R709X, Y569D. Analysis of the genetic association of the CFTR gene in children with cystic fibrosis showed that the CFTR-F508del mutation was the most frequent and reliable in 55% of children. Another risk mutation was CFTR-2143delt in 20% of children. All children with CFTR-F508del and CFTR-2143delT mutations were clinically characterized by severe cystic fibrosis.

Thus, cystic fibrosis develops against the background of unfavorable peri-and intra-natal periods, a hereditary complicated premorbid background, concomitant and past diseases, which can contribute to an unfavorable course of the disease.

Conclusion

The unfavorable premorbid background significantly affects the severity of the disease in children with MV. In children with cystic fibrosis, background complications are already a co-morbidity, significantly aggravating the course of the main pathology.

In the structure of the lower respiratory tract microflora in patients with cystic fibrosis, staphylococcus occupies a dominant position in 31 (26.0%) cases. Aureus, and 24 (20.0%) Pseudomonas aeruginosa.

3. The informative diagnostic aspects of patients with cystic fibrosis are the high frequency of mutations of the CFTR delF508 gene in the patients' genotype, which undoubtedly predisposes to the severe course of the disease with a genetic failure of the pancreas, the most common mutations of the CFTR-F508del, CFTR-2143delT, R709X, Y569D genes in Uzbekistan and the positive results of the sweat test, which made it possible to correct therapy in a timely manner.

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