

Complex Approach To The Diagnosis Of Cystic Fibrosis In Children

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ABSTRACT

*The aim of the study was to study the clinical and diagnostic features of cystic fibrosis in children in Uzbekistan. The study included 120 patients with cystic fibrosis at the age of 0 months. up to 14 years old, who were inpatient treatment in the department of pulmonology, pathology of early age and gastroenterology. In children with cystic fibrosis, the main clinical symptoms of 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 causative agents of the disease exacerbation were *S. aureus* - 32%, *Str. pyogenus* - 26%. Based on the results of the study, the frequency of mutations in the CFTR gene and their influence on the nature of the course were determined. A significant role has been revealed for the 4 most common gene mutations in Uzbekistan, CFTR-F508del, CFTR-2143delT, R709X, Y569D.*

KEY WORDS: *cystic fibrosis, molecular medicine, pediatrics, gene*

1. INTRODUCTION

The health status of children and adolescents is one of the most important indicators of the successful development of society and the state. According to V. Yu. Veltischev's definition, "Health is a state of life that corresponds to the biological age of a child, the harmonious unity of physical and mental traits, the formation of adaptive and compensatory reactions in the process of growth" [2]. Cystic fibrosis has recently taken one of the first places among hereditary diseases in children.

Cystic fibrosis is one of the most common monogenic human diseases. Determination of the frequency of mutations of a monogenic disease for specific populations makes it possible to optimize DNA diagnostics, reducing its cost and time [1]. Violation in the work of CFTR leads to the formation of thick, dehydrated secretions in several organ systems at once, however, changes in the bronchopulmonary system have the greatest impact on the course of the disease and are the main cause of mortality [4,7].

Cystic fibrosis is caused by mutations in a gene called the cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR gene controls secretory processes through mechanisms that are still poorly understood. The secretions of exocrine glands thicken, which leads to the development of a multisystem disease (with damage to the bronchopulmonary system, the digestive system, primarily the pancreas and liver, and the reproductive system) and, as a result, to premature death [3]. Typical clinical manifestations of the disease in

combination with a high content of sodium chloride in the secretion of sweat glands, as a rule, become the basis for the diagnosis of cystic fibrosis [5].

The life expectancy of such patients is closely related, first of all, with the preservation of respiratory function, which is seriously affected due to disorders of mucociliary clearance, which leads to the development of severe chronic respiratory tract infections from an early age and an increase in respiratory failure [8]. The leading role in the prognosis of the disease is played by the functional state of the bronchopulmonary system. In cystic fibrosis, local defense mechanisms are especially sharply weakened against the background of respiratory viral infections that "open the gate" for the penetration of pathogenic microorganisms - *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, etc. [9]. Most often, *S. aureus* becomes the first bacterial agent that affects the lower respiratory tract (most often it is sown from the sputum of children with cystic fibrosis during the first years of their life). Later, *P. aeruginosa* appears in the pathogenic microflora. We can already speak with confidence about the chronic colonization of the child's lower respiratory tract by these microorganisms [6].

The disease of cystic fibrosis often manifests itself in infancy. Despite the polymorphism of clinical manifestations, a triad of syndromes is typical: respiratory, intestinal (with typical stool) and dystrophic (by the type of hypotrophy). Often there is deformation of the fingers ("drum sticks") and nails ("watch glasses"), as a result of severe chronic hypoxia. Obstructive syndrome, whooping cough is typical. The liver and spleen are enlarged, rectal prolapse is characteristic. Stool in patients with cystic fibrosis is liquid, abundant, frequent, fetid. In the coprogram - steatorrhea, creatorrhea and very low fecal trypsin activity are expressed [5]. In our studies, we studied a comprehensive assessment of clinical and laboratory studies in children with cystic fibrosis in Uzbekistan.

The aim of our work is to study the clinical and diagnostic features of cystic fibrosis in children.

2. MATERIALS AND METHODS

We examined 120 patients aged 0 months. up to 14 years old, who were inpatient treatment in the department of pulmonology, pathology of early age and gastroenterology, in 15 of whom the diagnosis of cystic fibrosis was confirmed by clinical examination. And also in these children, a positive response to mucoviscidosis was by the method of determining immunoreactive trypsin.

The material for bacteriological examination was sputum, deep smears from the posterior pharyngeal wall, bronchial secretions during bronchoscopy. The data processing included the results of inoculations with a diagnostically significant titer (more than 10⁶ colony forming units).

Were analyzed for the presence of rare CFTR variants by massive parallel sequencing of the entire CFTR coding region and adjacent introns in combination with analysis of rearrangements within CFTR.

3. RESULTS AND DISCUSSION

An in-depth clinical and laboratory examination was carried out in the observed patients with cystic fibrosis. Among the children we observed, girls predominated. When studying the life history of children, the first symptoms of the disease on the part of the respiratory system were constant coughing, turning into a paroxysmal cough with difficult to separate viscous sputum in all patients. Dyspnea of a mixed nature was observed in 19.2% of children.

The severity of the course and outcomes of cystic fibrosis is significantly influenced by the timeliness of hospitalization and the provision of medical care. The observed children were admitted for treatment and examination at different times from the onset of the disease. So, in

16 (13.3%) cases, children were admitted to the hospital on the 3-5th day, 40 (33.3%) - on the 5th-7th days, and 64 (53.3%) patients were admitted to 8 or more days of illness after unsuccessful treatment at home.

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

Life history was carefully analyzed in all observed patients. The results of the analysis showed that the majority of patients with cystic fibrosis were born from pregnancy II-III - 58 (49%) and I - 45 (37.5%) pregnancies and from IV and more pregnancies - 17 (14.2%) children.

The severity of the disease in children is significantly influenced by an unfavorable premorbid background. Analyzing the background conditions of patients, we found that 112 (93.3%) children had anemia of I-II degree, allergic diathesis in 60%, residual rickets in 53.3% of patients, and hypotrophy in 73.3%. In children with cystic fibrosis, the background burdens are in fact already concomitant diseases that greatly aggravate the course of the underlying pathology.

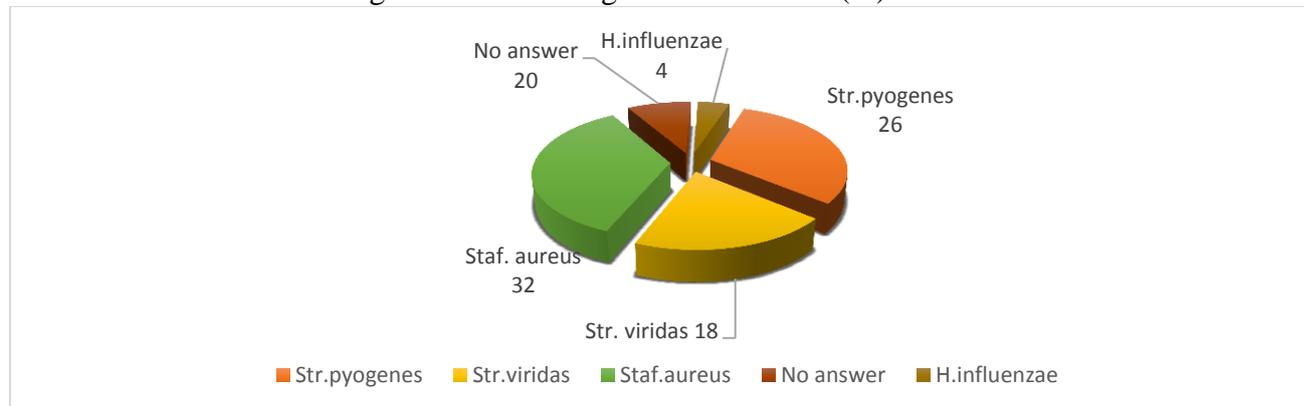
Upon admission to the hospital, the main complaints of parents of sick children were cough 107 (89.2%) paroxysmal, first dry, fatty stools 97 (81%), suffocation attacks 18 (15%), shortness of breath 54 (45%) of mixed nature, appetite 67 (56%), lethargy 54 (45%), pallor 112 (93%), sleep disturbance 51 (42.5%), runny nose 38 (32%).

Among 56 patients with cystic fibrosis, chronic bronchitis was found in 30 (53.6%), recurrent obstructive bronchitis - in 18 (32.5%), acute and recurrent pneumonia - in 29 (51.8%), bronchiectasis - in 6 (11, 6%), pulmonary bullae - in 1 (1.7%), prolapse of the rectal mucosa - 1 (1.7%), delayed physical development - in 30 (53.6%), 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 developing mucociliary insufficiency, disruption of the ciliated epithelium of the bronchial mucosa. Therefore, excessively viscous sputum stagnates in the respiratory tract, primarily in the small bronchi and bronchioles, mucostasis develops, then the bacterial flora joins and the inflammatory process begins.

Among 92 patients examined by us, MB in diagnostic titers in bronchial secretions during bacteriological examination of a smear from the pharynx was found that in 32% of cases st. Aureus, in 26% str. Pyogenes (Figure 1).

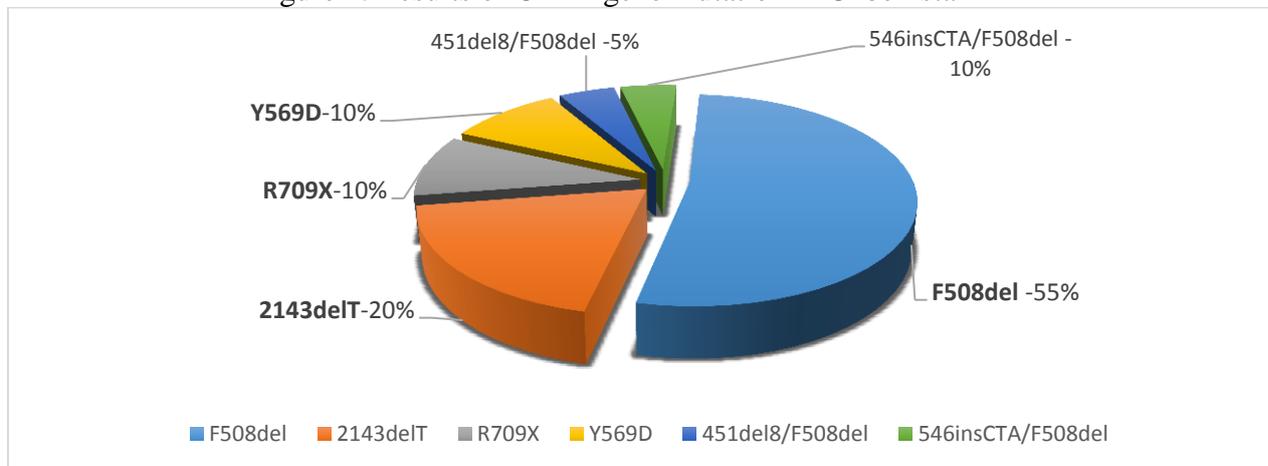
Figure 1. Bacteriological examination (%)



For the first time in Uzbekistan, we studied more than 2000 of the most frequent CFTR gene mutations associated with cystic fibrosis in 30 sick children, of which 4 reliably significant markers were identified: CFTR-F508del, CFTR -2143delt, R709X, Y569D. Analysis of the genetic association of the CFTR gene in children with cystic fibrosis, the CFTR-F508del

mutation was the most frequent and reliable in 55% of children. Another risk mutation was identified by CFTR -2143delT in 20% of children. All children with identified CFTR-F508del and CFTR-2143delT mutations were clinically characterized by severe cystic fibrosis (Figure 2).

Figure 2. Results of CFTR gene mutation in Uzbekistan



Thus, cystic fibrosis develops against the background of an unfavorable peri - and intrapartum periods, hereditarily aggravated by a premorbid background, concomitant and past diseases, which can lead to an unfavorable course of the disease.

4. CONCLUSION

1. The severity of the disease in children with cystic fibrosis is significantly influenced by an unfavorable premorbid background. In children with cystic fibrosis, the background burdens are in fact already concomitant diseases that greatly aggravate the course of the underlying pathology.
2. In the structure of the microflora of the lower respiratory tract in patients with cystic fibrosis, staf occupies a dominant position in 32% of cases. Aureus, and 26% str. Pyogenes.
3. Informative diagnostic aspects of patients with cystic fibrosis are the high frequency of mutations in the CFTR delF508 gene in the genotype of patients, which undoubtedly predisposes to a severe course of the disease with a genetically determined insufficiency of pancreatic function, a significant role has been revealed, 4 mutations of the CFTR-F508del gene that are most common in Uzbekistan, CFTR-2143delT, R709X, Y569D and positive sweat test results, allowing timely correction of therapy.

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Consent

Written informed consent was obtained from all participants of the research for publication of this paper and any accompanying information related to this study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

5. FINDING

No funding sources to declare.

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