PEDIATRICS

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CLINICAL CHARACTERISTICS OF CYSTIC FIBROSIS IN CHILDREN IN KHARKIV REGION

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Abstract: The article deals with the study of clinical and paraclinic peculiarities of CF (including respiratory tract microbiocenosis) in children in Kharkiv region. The study also involves the assessment of microbiological status correlation in patients with CF and the disease incidence. The study implied examination of 30 children with cystic fibrosis. They underwent clinical, paraclinical (bacteriological examination of sputum and epithelial lining fluid, chest X-ray, CT scan of lungs) examination. Clinical and paraclinic (bacteriological examination of sputum and epithelial lining fluid, chest X-ray, CT scan of lungs) examination was performed. The study showed that CF severity in patients was associated with chronic P. aeruginosa and B. cepacia infection. None of the patients in Kharkiv region was found to have any of pathognomonic respiratory causative microorganisms, such as M. Tuberculosis and non-tuberculous micobacteria, H. influenza, Ralstonia picketi, and P. Aeruginosa infection was not identified which can be the evidence of insufficient laboratory diagnosis.

KeyWords: cystic fibrosis, children, microflora.

INTRODUCTION

Cystic fibrosis (CF) is one of the most frequent lethal genetic disorders of autosomal recessive nature. The assumed prevalence of CF in Ukraine is one case per 2.300 of newborns. CF patients' life expectancy worldwide is 38 years. It is unknown for Ukraine, but the age of the oldest member of Kharkiv CF Association is 35 years [1, 2, 7].

CF develops in mutation of gene, coding the cystic fibrosis transmembrane conductance regulator – CFTR, which is in the sevenths human chromosome. In respiratory CFTR defect results in high bronchial mucous viscosity, mucociliary clearance decrease and development of chronic bronchopulmonary infection from the first months of child's life. Damage of respiratory tract in CF is the main cause of death [3, 4, 5, 8].

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The basic respiratory tract microflora in CF is Staphylococcus aureus (S. aureus) in the initial period, then Haemophilus influenza (H. Influenza) and Pseudomonas aeruginosa (P. aeruginosa). In recent years, the role of Burkholderia cepacia (B. Cepacia), Nontuberculous mycobacteria, Stenotrofomonas maltophilia (S. Maltophilia), Alcaligenes xylosoxidans (A. xylosoxidans), Aspergillus sp. and others has increased.

CF clinical presentation and prediction are significantly defined by bacterial composition of the respiratory tract. Thus, trials with mice demonstrated that combined infection, induced by P. aeruginosa and B. Cepacia, enhances virulence properties of causative agents and all the animals die within one day. Mutual virulence enhancement of P. aeruginosa and B. cepacia bacteria in vivo provides the possibility of mutual use of the "Quorum sensing" system components by closely related bacteria. There is evidence that over 80% of clinical isolates of B. cepacia are able to form a biofilm and colonize the tissue surface, to form permanent infection reservoirs in hospital environment, and this contributes to bacteria persistence to eradication by phagocytes and elimination in antibiotic therapy. In

each country and region, the data on microbial flora and resistance in children with CF are different, and this is related to differences in CF genotype in population, in antibacterial therapy algorithms, drug availability, economic condition and national peculiarities [6, 9, and 10].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

1. To study clinical and paraclinic peculiarities of CF in children (including respiratory tract microbiocenosis) in Kharkiv region.
2. To define correlations of microbiological status in patients with CF with the disease morbidity.

2.2 Subjects & Methods

The study involved examination of 30 children with CF at the Pulmonology Department of Regional Children's Clinical Hospital No. 1. Of them, 23 children (12 boys and 11 girls) with CF underwent complete physical examination in 2014. Clinical and paraclinic (bacteriological examination of sputum and epithelial lining fluid, chest X-ray, CT scan of lungs) examination was performed.

In statistical analysis of paraclinic data (bacteriological studies, tomography) for increase of study informative value, we analyzed the findings, received not only in MHCI RCCH No. 1, but the data from records, made in other Kharkiv clinics for the last 5 years. Chronic colonization of P. Aeruginosa was determined in two-fold identification of causative microorganism in bacterial inoculation during 6 months.

Statistical data processing was performed using MS Excel and Statgraphics-5 software. The study was conducted in accordance with basic ethic and legal principles of European Convention for the Protection of Vertebrate Animals (Strasbourg, March 18, 1986), EEC Directive for the Protection of Vertebrate Animals (Strasbourg, November 24, 1986), ICH GCP (2008), GLP (2002) and national regulations.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Prenatal CF diagnosis was made in 2 (8.7± 5.9) % of children, 12 (52.1±10.4) % of children were diagnosed in the first year of life, 10 (43±10.1)% – in preschool period, 1 (4 %) child was diagnosed at early school age.

The main clinical CF signs included symptoms of bronchopulmonary and gastrointestinal impairment, as well as nutritional disorders. The following presentation was observed in bronchopulmonary abnormalities: chronic cough with viscous sputum discharge, airways obstruction, radiologic abnormalities in lungs (bronchiectasis, infiltration, pneumosclerosis); nasal polyps, maxillary sinus conditions; drumstick fingers and watch-glass nails symptoms.

The group of patients with severe CF included 8 children (4 boys and 4 girls). In the group of patients with severe CF: prenatal diagnosis of the main condition was determined in 1 (12.5±6.7)% child, at the age under 1 year – in 7 (87.5 ± 6.9)% children. The following main clinical signs in the group of patients with the severe disease were observed: chronic pancreatic deficiency – in 8 (100 %) children, diffuse pulmonary fibrosis – 8 (100%), extensive bronchiectasis – 6 (75±15)%, chronic obstructive bronchitis – 5 (62.5±10)%, chronic II stage respiratory insufficiency – 6 (75±15)%, I stage pulmonary hypertension was observed in 5 (62.5±10)% children. The patients were found to have such complications of the main condition as cirrhosis, macronodular type, portal hypertension (1 patient); allergic bronchopulmonary aspergillosis (1 child); extensive subcutaneous emphysema (1 child).

The following CF-specific respiratory pathogens were detected in sputum culture in 23 children, who were treated in the Pulmonology Regional Children's Clinical Hospital No. 1. 23 in 2014: P. aeruginosa – in 13 (56.5 ± 10.3)% of children, in (80.9 ± 8.1)% of cases large colony

growth was observed, with moderate growth in (19.1 ± 8.1)%; S. aureus – in 10 (43.4 ± 10.3)% of patients, B. cepacia in (13 ± 7) % of patients, S. maltrophilia – in 1 (4 %), Acinetobacter – in 1 (4 %), A. xylosoxidans – in 2 (8 %), Candida – in 16 (70 ± 9.5)% of children.

More than in 2/3 cases chronic lung infections was induced by association of microorganisms rather than by pure culture, in most cases – by more than three microorganism species. The most frequent association involved combination of P. aeruginosa + S. aureus in (22 ± 8.6)% of patients, and P. aeruginosa + B. cepacia in (13 ± 7)% of patients. Except P. Aeruginosa, 4% of patients were found to have such nonfermentative gram-negative microorganisms as S. maltophilia.

In the group of patients with severe conditions chronic P. Aeruginosa colonization was observed in 8 (100 %) children, in 4 (50 ± 17,6)% of them – together with S. aureus, S. maltrophilia (1), Acinetobacter (1), A. xylosoxidans (2), B. cepacia complex – in 3 (37,5 ± 17,1) %. The earliest age of the observed chronic colonization was 6 months.

Comparison of microbiological status in patients with moderate and severe CF is presented in Table 1.

Table 1.

Respiratory microbiological status of patients with moderate and severe cystic fibrosis

Causative agents	Severity	
	Severe, n=8, n (%)	Moderate, n=15, n (%)
Pseudomonas aeruginosa	8 (100)*	4 (27 ± 11.4)
Pseudomonas aeruginosa resistent	4 (50 ± 17.7)*	0
Staphylococcus aureus	4 (50 ± 17.7)	7 (47 ± 12.9)
Stenotrophomonas maltrophilia	1 (13 ± 11.9)	0
Acinetobacter	1 (13 ± 11.9)	0
Alcaligenes xylosoxidans	2 (25 ± 15.3)	0
Bulkholderia cepacia complex	3 (37 ± 17.1)*	0

Note: * - differences in the incidence of causative microorganisms in the groups are statistically significant ($p < 0.05$).

Thus, P. aeruginosa, B. Cepacia were significantly more frequent in the group of patients with severe CF. Determination of these infections in CF patients' sputum may be the adverse prognostic factor for the disease severity. Multi-drug resistant strains of P. Aeruginosa were observed in the groups of patients with severe CF in 50% and significantly more frequent, than in the group of children with moderate severity. Candida was determined in 16 (70%) children.

Our data are slightly different from the data received by Moscow N. I. Kapranov CF center, where S. aureus was determined in 64.1 % of cases, P. aeruginosa in 64% and B. cepacia – in 48.9% of patients. In Moscow CF center B. cepacia was observed significantly more often, and this may be related to the improved diagnosis of this pathogen [3, 4, 10].

Comparing our findings to the data of the world CF centers we should mention that the USA Registry takes into account not only the frequency of the above listed microorganisms, but H. influenza, multi-drug resistant strains of S. aureus and P. Aeruginosa are considered separately. The Registry of Great Britain monitors the plating of fungi of Aspergillus fumigatus species from the respiratory tract. The French Registry involves information about patients, discharging M. Tuberculosis from their airways. Non-tuberculous micobacteria are plated in 7.1% cases in Israel. Perhaps, the facilities of Kharkiv region clinics do now provide a possibility of accurate identification of these pathogens [3, 4, 10].

Additionally, in Kharkiv region mucoid and non-mucoid strains of pseudomonas infection are not types, such pathogen, as Ralstonia picketi, described in CF is not defined; none of the laboratories defines the level of antibodies to P. Aeruginosa, and this is necessary to determine the infection condition, period/phase of the disease, and to define the antibacterial therapy algorithm. Thus, Lee at al., 2003 determined 4 patient's conditions dependable on P. aeruginosa introduction of infection:

1. Chronic infection – in determination of P. aeruginosa in more than 50% of sputum culture and presence of

increased titer of precipitating antibodies to P.aeruginosa.

2. Intermittent infection – in determination of P. aeruginosa in 50% examinations during one year in normal titers of precipitating antibodies to P.aeruginosa.

3. Absence of infection – when the patient, infected by P. Aeruginosa, has no determined causative microorganism in bacteriologic sputum in the course of 12 months.

4. Never infected – P. aeruginosa has never been determined in sputum, and there are no antibodies.

The abovementioned problems with laboratory diagnostics of the infection complicates the work of the clinicians, and is the objective prerequisite for diagnostic errors and incorrect approach to prescription of antibacterial therapy of pseudomonas infection in children with CF.

4 CONCLUSIONS

1. CF severity in patients is associated with chronic infection by P. aeruginosa and B. cepacia.

2. None of the patients in Kharkiv region was found to have any of pathognomonic respiratory causative microorganisms, such as M. Tuberculosis and non-tuberculous micobacteria, H. influenza, Ralstonia picketi, and P. Aeruginosa infection was not identified, which is the evidence of insufficient laboratory diagnosis.

3. It is necessary to improve laboratory diagnosis for determination of respiratory pathogens and their susceptibility to increase the quality of medical care for children with CF and substantiated prescription of antibacterial therapy.

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