ejpmr, 2019,6(12), 130-133

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ASSESSMENT OF HEREDITARY WEARING IN CHILDREN WITH CHRONIC BRONCHOPULMONARY PATHOLOGY

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Article Received on 03/10/2019 **Article Revised on 23/10/2019** **Article Accepted on 13/11/2019**

ABSTRACT

Background: Hereditary lung diseases represent one of the most complex diagnostic, pathogenetic and therapeutic problems of modern pulmonology. Currently, due to the expansion of clinical and diagnostic capabilities for monitoring the effectiveness of various therapeutic effects and the growth dynamics of bronchopulmonary pathology in children, the study of heredity in the occurrence of chronic respiratory diseases is of particular importance, which will improve their early detection in risk groups using modern high-tech methods and diagnostic tools. **Objective:** Determine the genetic predisposition of chronic bronchitis in schoolchildren in Uzbekistan. **Methods:** To fulfill the goal of the thesis, 150 sick children with chronic diseases of the bronchopulmonary system were selected, who received treatment in the pulmonology department of the Republican Specialized Scientific and Practical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan and the Bukhara Regional Children's Multidisciplinary Medical Center. **Results:** Genotyping results based on the case-control analysis method showed that among children with chronic bronchitis a heterozygous carriage of mutations of the CFTR_F508del / n, CFTR_W1282X / n, CFTR_W1282X / n, CFTR_N1303K / n gene was detected. Mutation CFTR_F508del / n was detected in 6.25% (3 children), CFTR_W1282X / n in 2.1% (1 child), CFTR_N1303K / n in 2.1% (1 child). **Conclusion:** Thus, the association of markers F508del, W1282X, N1303K of the CFTR gene established in our studies confirms the data of various authors that in patients with severe chronic diseases of the respiratory tract and lungs, mutations of the CFTR gene, especially the deletion of F508 in the heterozygous state, have been increasingly found recently (T.E. Ivashchenko, V.S. Baranov, 2002).

KEYWORDS: Chronic bronchitis, children, the CFTR gene mutation.

BACKGROUND

Currently, due to the expansion of clinical and diagnostic capabilities for monitoring the effectiveness of various therapeutic effects and the growth dynamics of bronchopulmonary pathology in children, the study of heredity in the occurrence of chronic respiratory diseases is of particular importance, which will improve their early detection in risk groups using modern high-tech methods and diagnostic tools.[1,9]

Chronic bronchitis is a widespread, but still little studied disease. This disease belongs to the group of chronic obstructive pulmonary diseases along with emphysema and bronchial asthma. At the same time, the issues of etiology, pathogenesis, early diagnosis and treatment are still underdeveloped, occupy many researchers and continue to be vividly debated. In Uzbekistan, chronic bronchitis (CB), in the structure of chronic obstructive pulmonary disease (COPD) is 70 - 85%. In terms of prevalence, CB takes the 1st place among lesions of the lower respiratory tract and amounts to 1,550. per 100 thousand people. According to domestic data, chronic obstructive bronchitis among all diseases of the bronchopulmonary system causes death in 80% of cases and disability in 50%.

Hereditary lung diseases represent one of the most complex diagnostic, pathogenetic and therapeutic problems of modern pulmonology. Recognition of these diseases is associated with considerable difficulties. Often they are mistaken for the usual forms of chronic non-specific lung diseases.

However, a clear definition of the true nature of the pathological process ensures the success of therapeutic measures. N.P. Bochkov and co-authors emphasized that recurrent and chronic, long-term untreatable diseases, especially in childhood, often include the number of hereditary forms of pathology.[4] This provision is also true for bronchopulmonary diseases.[4,6]

Among the genetically determined diseases, the clinical picture of which is determined by the defeat of the bronchi and lungs, a special place is occupied by cystic

fibrosis (CF) (OMIM 219700), characterized by an autosomal recessive type of inheritance. Among children with chronic and recurrent diseases of the bronchopulmonary system, CF is detected in 14.5% of cases.[4,6]

Cystic fibrosis is the most common hereditary disease caused by mutations in the CFTR gene, a cystic fibrosis transmembrane conductivity regulator. The CFTR protein, functioning as a cAMP-dependent channel, regulates the activity of other chlorine and sodium channels, participates in water and ATP and performs a number of other important functions (N.Yu. Kashirskaya et al., 2012, No. 1). In this disease, the whole organism is involved to one degree or another in the pathological process, but to a greater extent - the respiratory system.[1,2]

Due to the widespread genetic polymorphism, the clinical picture of CF can be erased and atypical. In this connection, it is necessary to conduct differential diagnosis of CF in bronchopulmonary lesions such as repeated and recurrent pneumonia with a protracted course, extended bronchiectasis, bronchial asthma, chronic recurrent bronchitis and bronchiolitis.

As is known in most patients, symptoms of CF appear already in the first year of life. Only in very rare cases, the diagnosis of CF is not established until patients reach school age, which may be due to “soft” mutations and the relative safety of the pancreas.[2,4]

On the recommendation of the International Consensus on CF [2011] - every child with asthma and recurrent bronchitis, accompanied by changes in the radiograph and signs of infection, should be sweat tested.

In connection with the above, in order to exclude CF in the risk group of children with chronic bronchopulmonary pathology, molecular genetic tests were conducted as part of our studies. It should be noted that when working with questionnaires of patients with chronic bronchopulmonary pathology with a primary diagnosis upon admission to the emergency department in 16 children, the primary diagnosis of pulmonary CF and bronchopneumonia was called into question. Further, during the examination in the department of pulmonology, it was not confirmed (by sweat test, general and biochemical analysis of blood and feces, ultrasound diagnostics and radiography) and the diagnosis at discharge was made as recurrent or chronic bronchitis.

THE AIM OF THE STUDY

Determine the genetic predisposition of chronic bronchitis in schoolchildren in Uzbekistan.

MATERIAL AND METHODS

To fulfill the goal of the dissertation, a contingent of sick children with chronic diseases of the bronchopulmonary system was selected, who received treatment in the pulmonology department of the Republican Specialized Scientific and Practical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan and the Bukhara Regional Children's Multidisciplinary Medical Center.

In the laboratory of human genomics of the Institute of Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan, molecular genetic studies were conducted to study the polymorphism of the CFTR gene in children with chronic bronchitis and bronchial asthma.

A total of 150 children were examined and all underwent clinical and genealogical research. The clinical-genealogical method is a method of analyzing pedigrees that allows you to trace the nature of the transmission of any trait or illness in the family, taking into account the type of family ties between members of the pedigree. The collection and analysis of the pedigree is an important stage in the examination of the patient, allowing you to establish the hereditary nature of the disease in the practice of doctors of all specialties. For research, we used the method of questioning patients.

Of the 150 children examined by us with chronic bronchitis and bronchial asthma, 48 people with a moderate to severe course of the disease were selected for genetic research. The control group consisted of 60 healthy children. In order to study the genetic contribution of the CFTR gene to the development of chronic bronchitis in children, we analyzed the 8 most frequent mutations of the CFTR gene associated with CF.

Genotyping was carried out by RT - PCR using reagents "RPA DNA - Technology" and "Synthol" (Moscow, RF). A polymerase chain reaction was carried out with real-time detection of the results, analysis of the melting curves and the "end point", and qualitative analysis. The results obtained were processed statistically in accordance with the observed frequency distributions of the genotypes theoretically expected according to the Hardy-Weinberg equation using the $\chi 2$ criterion. When pairwise comparing the frequencies of genotypes and alleles with each other, the exact Fisher test was used. To assess associations, the relative risk of OR was calculated using the formula OR = ad / bc, where: a - the number of individuals with the presence of the analyzed marker among patients; b - the number of persons with its absence; c and d are the number of individuals, respectively, with the presence and absence of a marker in the control group. A value of OR = 1 indicates a lack of association, OR> 1 - occurs with positive association (risk factor) and OR <1 - negative association of the allele with the disease.

RESULTS AND DISCUSSION

An analysis of hereditary burden for diseases of the upper and lower respiratory tract showed that a history of bronchopulmonary pathology was not burdened in 66.7% of parents of probands of both groups.

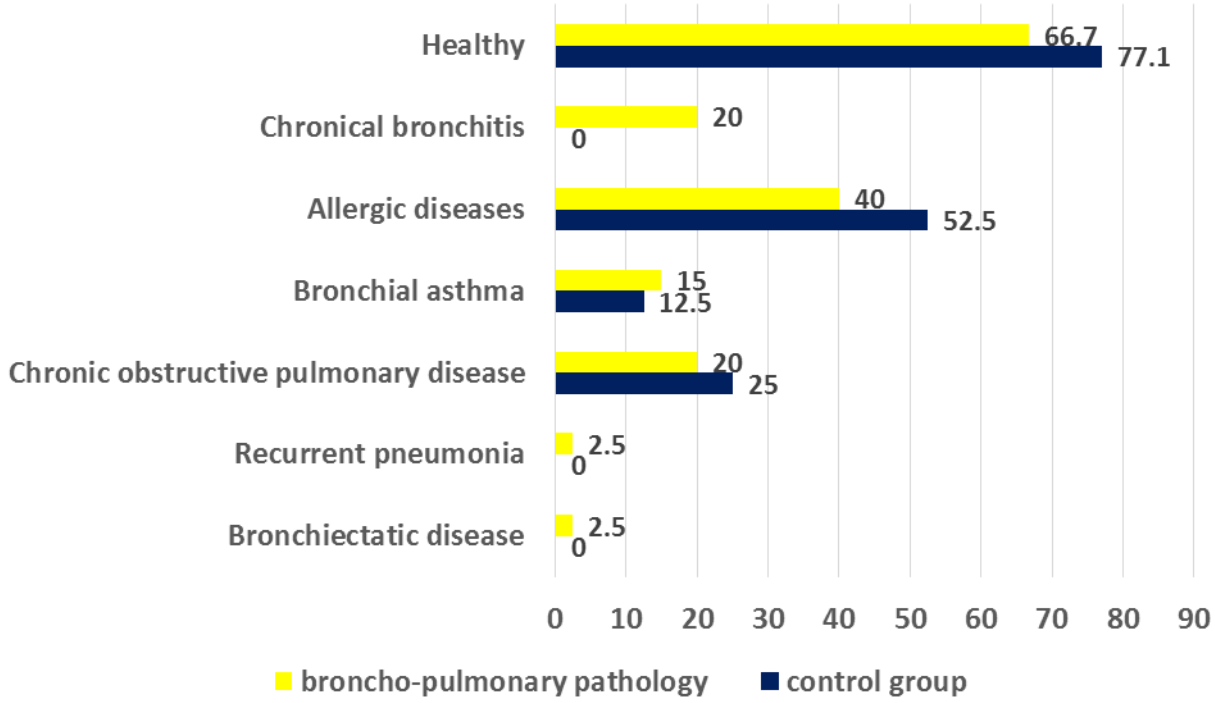

Fig. 1: Indicators of clinical and genealogical research, respiratory diseases proband, %.

The results of this study reliably revealed a hereditary predisposition to the development of chronic bronchitis and bronchial asthma in 32.3% of the parents of patients of the examined groups.

Comparison data of the two groups on the burden of bronchopulmonary pathology are presented in the diagram. As can be seen from the above data, chronic bronchitis occurred in the history of parents in 20.0% of cases. Allergic diseases are widespread today, the frequency of which in this sample was 40.0% in the main group and 62.5% in the control group (Fig. 1).

Genotyping results based on the case-control analysis method showed that among children with chronic bronchitis a heterozygous carriage of mutations of the CFTR_F508del / n, CFTR_W1282X / n, CFTR_W1282X / n, CFTR_N1303K / n gene was detected. Mutation CFTR_F508del / n was detected in 6.25% (3 children), CFTR_W1282X / n in 2.1% (1 child), CFTR_N1303K / n in 2.1% (1 children) (Table).

Table 1: The frequency of occurrence of heterozygous mutations of the CFTR gene in children with chronic bronchitis compared with the control group.

Diagnosed mutations in the CFTR gene	Cases (48)	Control (60)	$\chi 2$	pvalue
CFTR_F508del	0.045	0	3.06	0.04
CFTR_G542X	0	0	0	1
CFTR_W1282X	0.015	0	1.02	0.11
CFTR_N1303K	0.015	0	1.02	0.11
CFTR_2143delT	0	0	0	1
CFTR_2184insA	0	0	0	1
CFTR_3849+10kbC> T	0	0	0	1
CFTR_dele 2,3 (21kb)	0	0	0	1

CONCLUSION

Thus, the association of markers F508del, W1282X, N1303K of the CFTR gene established in our studies confirms the data of various authors that in patients with severe chronic diseases of the respiratory tract and lungs, mutations of the CFTR gene, especially deletion of F508 in the heterozygous state, are increasingly found recently (T.E. Ivashchenko, V.S. Baranov, 2002).

In order to finally assess the importance of the genetic factor in the development of chronic bronchitis, in the future it is necessary to expand the list of candidate genes for the development of predictive medicine. Due to the large number of mutation variants in the CFTR gene, the possibility of the presence of unidentified mutations in the examined patients cannot be ruled out.

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