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APPLICATION OF MODERN MOLECULAR GENETIC METHODS FOR THE DIAGNOSIS OF COMPOUND HETEROZYGOUS GENOTYPES IN PATIENTS WITH CYSTIC FIBROSIS

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Introductions. Cystic fibrosis (CF) is the most common monogenic disease with an autosomal recessive type of inheritance and is characterized by damage to the glands of external secretion (mainly respiratory and digestive systems). The disease was first described by Swiss pediatricians Fankoni G., Uhlinger E. and Knauer C. in 1936. Farber S. in 1943 proposed the name "cystic fibrosis" (from mucus – mucus and viscus – "bird glue"). In 1989, a gene was isolated, and later the structure was deciphered and the function of the protein, the primary product of the gene, was determined. CF has been shown to be caused by a mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. The population frequency in the European population is 1 : 1500-2500, in Ukraine there is 1 : 2200 among newborns. Women

with CF are more likely than men to suffer from pulmonary form and have a shorter life expectancy. The average life expectancy of CF patients in the world is about 37 years, in Ukraine – only 16 years. The introduction in recent decades of neonatal screening in combination with molecular genetic methods allow early diagnosis of CF, which in combination with modern treatments significantly improves the prognosis for life in these patients.

Aim. Rationale for the use of modern molecular genetic methods for the diagnosis of compound heterozygous genotypes and prevention of cystic fibrosis in such families.

Materials and methods. Clinical and genealogical, biochemical, molecular genetic, instrumental.

Results and discussion. The use of molecular genetic methods allowed to diagnose this disease much earlier. The gene is located on chromosome 7 and synthesizes the transmembrane regulatory protein CF CFTR, which is involved in the action of chlorine ion transport channels in the cell membranes of the endocrine glands. The cause of pathological changes in CF is the presence of mutations in both alleles of the gene located on the long arm of chromosome 7(7q31). This gene has 27 exons and controls the synthesis of CFTR, which functions as a cyclic adenosine monophosphate-regulated chlorine channel on the apical surface of epithelial cells. To date, 1864 mutations are known, which are divided into 5 classes: Class I – mutations associated with impaired CFTR protein synthesis (including G542); Class II – mutations associated with abnormalities in the structure of the protein (including delF508); Class III – impaired gene expression at the level of the cell membrane, in which there is dysregulation of the function of membrane channels for chlorine (G551D); Class IV – dysfunction of chlorine ion channels (R117H); Class V – mutations that cause a decrease in the amount of protein, its synthesis is blocked at the level of the precursor protein. Class I-III mutations are "severe", IV-V – "soft". It should be noted that most of the mutations are quite rare and occur in isolated cases in individual populations and ethnic groups. "Major" mutations have diagnostic value: W1282X; G542X; N1303K; G551D, the frequency of which in European

populations ranges from 3% to 5%. The prevalence of the delF508 mutation in Europe corresponds to a distribution gradient: it increases from Southeast to Northwest and ranges from 22% in the Ashkenazi Jewish population and to 90% in Denmark. In Ukraine, the frequency of this mutation is 49%, the frequency and spectrum of other mutations in the CFTR gene among patients with CF in the Western region of Ukraine: W1282X – 3.2%; G542X – 2.4%; N1303K – 2.4%; CFTRdele2.3 – 1.6%. The third most common mutation, G542X, is also called the Phoenician mutation and is more common in southwestern European populations. Severe hepatic impairment associated with pancreatic insufficiency and moderate pulmonary disease in patients with this mutation have been reported. Prior to the discovery of the gene, genetic counseling for this disease was to perform a standard risk calculation according to the autosomal recessive nature of the inheritance of this disease, followed by informing the family about the high genetic risk of rebirth of a sick child. The diagnosis of CF is based on typical pulmonary manifestations, symptoms of gastrointestinal lesions, family history and positive results of sweat chloride studies, as well as molecular genetic studies.

Here is a case of cystic fibrosis in a 7-year-old girl. The child's parents consulted a pediatrician with complaints of recurrent rhinosinusitis, abdominal pain, recurrent vomiting. The reason for consulting a geneticist was to clarify the diagnosis.

The girl was born from the IV-th pregnancy, which proceeded without features, at 36-37 weeks of gestation, II childbirth with signs of asymmetric hypotrophya. Despite twice a positive neonatal screening for CF (increase in the level of immunoreactive trypsin by 10 times), the parents refused further examination at that time. Sweat chlorides – 22-26 mEq/l at the age of 3.5 months; 42.8 mEq/l – at 6 years. Pancreatic elastase in feces – more than 200 μg/g of feces.

The patient's condition on examination of moderate severity due to moderate nasal obstruction and functional disorders of the stomach. Physical and mental development correspond to age. Deformed phalanges of the fingers. Nasal breathing is difficult, the throat is swollen, the tonsils are hypertrophied, moderately hyperemic.

At auscultation of lungs breath is carried out in all departments, rales are not listened. The chest is deformed, with signs of rickets. Percussion sound is normal, symmetrical. From internal organs without pathology. Body weight – 20.2 kg, height – 121 cm. BMI – 13.79 kg/m2. Sat O2 – 98-99%. BH – 20/min. Heart rate – 99/min. Blood pressure – 90/52 mm Hg. X-ray of the lungs and heart: the pulmonary pattern is enhanced, the roots are small, with circular shadows of the bronchi in frontal section. The sinuses are free. The domes of the diaphragm are clear and smooth. The heart has not changed in size. Examination by an ENT doctor: chronic rhinitis. Hypertrophy of the tonsils of the second century. Adenoids of the I-II centuries.

To confirm the patient's CF, DNA was isolated and the CFTR gene was examined for specific mutations by PCR and subsequent heteroduplex analysis or RFLP (restriction fragment length polymorphism). Mutations *R117H*, *F508del*, *ΔI507, F508C, 1677delTA, CFTRdele2, 3 (21kb)* and polymorphism of the *IVT8 polyT locus (5T / 7T, 9T)* were analyzed. Results of a molecular genetic study of the family: proband is a heterozygous compound for *F508del* and *R117H* mutations. The mother is a heterozygous carrier for the *R117* mutation. The father is a heterozygous carrier for the *F508del* mutation.

Conclusions. Active detection of heterozygous carriers followed by medical and genetic counseling, monitoring with a computer DNA data bank can be a rational and highly effective way to prevent this serious inherited disease. Early diagnosis of CF is directly related to a better prognosis for the course of the disease. In turn, prenatal diagnosis and medical and genetic counseling are the main measures to prevent the birth of patients with CF. Combining the efforts of specialists in pediatric clinics, geneticists, molecular biologists, specialists in prenatal diagnosis contributes to a comprehensive solution to the problems facing families with children with CF.