FEATURES OF NEUROLOGICAL DISORDERS IN CYSTIC FIBROSIS

Omonova Umida Tulkinovna[1], Khaitbaeva Nargiza Temurovna[2]
[1]Tashkent Pediatric Medical Institute
[2]Republican Specialized Scientific and Practical Medical Center for Maternal and Child Health
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Abstract*. This article analyzed literary information about the features of the development of neurological disorders in cystic fibrosis (CF), about modern views on the early diagnosis of this pathology. A generalized analysis of scientific foreign and domestic literature shows that this problem still has a number of complex unresolved issues. Integrating mental health screening, early detection of neurological disorders, and targeted treatment of patients with CF may reduce the mortality and disability observed in this disease.*

Keywords*: cystic fibrosis (CF), CFTR protein, monosymptoms, T2 relaxometry procedures.*

Cystic fibrosis (CF) is an autosomal recessive monogenic hereditary disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes the functioning of the CFTR protein - a chloride channel on the membranes of most epithelial cells. The gene is located on the long arm of chromosome 7, includes 27 exons and regulates the functioning of ion channels and membrane transport in epithelial cells of the respiratory tract and exocrine glands, in particular the pancreas [1,4,6].

The incidence of cystic fibrosis varies across countries, from 1 in 1,800 in Ireland to 1 in 26,000 births in Finland [2, 4, 5]. The incidence of CF in the European population ranges from 1:600 to 1:17000 newborns. In the USA, the number of people with CF reaches more than 30,000, and around the world – 80,000–100,000 people [3,9,11]. The 2019 Russian registry presents data on 3169 patients with CF from 81 regions of the Russian Federation [2,3,5]. According to the national CF registry of the Russian Federation for 2021, the average age of death is 23.7 ± 10.3 years, the average age of patients is 14.0 ± 9.8 years. The disease is considered as a model of accelerated aging [1,2].

CF is a complex disease that affects many organs. The target organs are the bronchopulmonary system, pancreas, liver and biliary tract, intestines, etc. Although the nervous system is not traditionally considered as an organ affected by CF, foreign scientists prove that it is affected and can contribute to the pathogenesis of CF [11, 16,18]. It is generally accepted that chloride transport significantly alters neuronal activity, suggesting that the presence or absence of CFTR in the nervous system may influence neuronal function. Although CFTR is commonly found on epithelial cells of the respiratory tract, gastrointestinal tract, pancreas, vas deferens, and sweat glands, there is evidence that CFTR is present in the brain and spinal cord [8,14]. The distribution of CFTR in the brain was initially thought to be limited to the hippocampus, but its expression is now known to be widespread in neuronal cells throughout brain tissue [13,18,19]. The fundamental consequences of CFTR mutation on CNS function are currently unknown. CFTR has been found to be widespread in the early stages of neuronal development, and delayed maturation of brain structures has been identified in people with CF. In addition, CFTR expression in the

hypothalamus appears to be decreased in people with Alzheimer's disease compared to controls [7, 8].

The clinical picture of CF is diverse, which is explained by the large number of mutations in the CFTR gene. Cystic fibrosis can occur under the guise of various diseases of the lungs, liver, and pancreas. There are patients with monosymptoms in the form of persistent polyposis sinusitis or in the form of male infertility in men with CF. But most people with CF have varying degrees of impaired nutritional status [3,5]. CFTR gene mutations are divided into 6 classes, which determine the severity of the clinical picture of the disease at the protein level. It is generally accepted that mutations of classes I–III lead to severe disruptions in the functioning of the CFTR protein – to the classic phenotype of cystic fibrosis, while mutations of classes IV–VI cause partial "mild" dysfunction of the transporter, which is clinically manifested in milder forms of the disease [6,10,11].

In addition to classic respiratory and autonomic problems, patients with cystic fibrosis experience a variety of symptoms, including behavioral and cognitive dysfunction. Psychological adaptation of children with cystic fibrosis is longer and has a number of features due to a complex of psychological qualities characteristic of such patients (increased anxiety, aggressiveness, negativism, emotional tension, inadequate self-esteem, etc.). This suggests that brain damage, which can be examined using non-invasive magnetic resonance imaging (MRI), is a manifestation of this condition. However, the integrity of brain tissue in regions regulating cognitive, autonomic, respiratory, and mood functions in CF patients is unclear. The researchers assessed regional changes in the brain using high-resolution T1-weighted gray matter (GM) density-based imaging and T2 relaxometry procedures in CF compared with controls. People with chronic illnesses such as CF were at increased risk of depression and autonomic dysfunction. In addition, many aspects of the disease itself can lead to high levels of anxiety. In addition, the literature reports significantly higher BAI and BDI-II scores in CF patients compared to healthy controls, which is consistent with previous studies [12,16, 17]. Additionally, the researchers found that CF patients had lower overall MoCA scores, and this change was most significant in the visuospatial/executive subdomains. Several brain regions, including the cerebellum, hippocampus, amygdala, insula, prefrontal, and temporal regions, showed tissue changes based on GM density or T2 relaxometry procedures, regions that are involved in cognition, mood, and autonomic function. Neuronal damage caused by hypoxia and/or hypercapnia is considered one of the key mechanisms of pulmonary diseases [12, 17]. Both hypoxia and hypercapnia are often present in patients with CF along with a mutated CFTR gene and are potential causes of the observed changes in the nervous system.

Currently, an important goal in the treatment of cystic fibrosis is to slow the progression of bronchopulmonary disorders, since deterioration of lung function primarily leads to a decrease in the quality and life expectancy of these patients [15].

Studies have shown that exacerbations of pulmonary infections lead to a significant decrease in health-related quality of life in patients with CF [4].

Moreover, regardless of whether intensive antibiotic therapy is carried out in a hospital setting or at home, aggressive treatment of exacerbations of pulmonary infection leads to a significant improvement in quality of life [6,10], as well as an increase in life expectancy [8].

Treatment of chronic Pseudomonas infection with inhaled tobramycin [11] or aztreonam [15] also results in improvements in health-related QOL as well as FEV1.

The use of physiotherapeutic methods aimed at clearing the airways of accumulated sputum and mucus 30 is characterized by a low level of patient adherence in the long term, as it requires 20 to 45 minutes twice a day [4].

Methods used in clinical practice demonstrate short-term effectiveness, but their impact on health-related QoL has not been assessed in well-designed studies. Pharmacological agents to restore mucociliary clearance of the airways include DNase, β2-agonists delivered by nebulizer, and inhaled hypertonic NaCl solution. Although the safety and effectiveness of the above methods have been confirmed in randomized controlled trials, there has been no convincing evidence of improvement in health-related quality of life in patients with CF [13].

The assessment consists of eight indicators: vision, hearing, speech, ambulation, fine motor skills, emotions, cognitive processes and pain level. Each indicator has five or six gradations [15,19].

A multivariate utility function is used to assign a specific importance to each attribute level. Using a special formula, the resulting values, when combined, provide an overall utility that provides a comprehensive assessment of the patient, facilitating the assessment of the various consequences of the disease and the various degrees of severity of the disease. In the USA, studies were conducted on adolescents with CF using the HUI questionnaire, and the results were obtained on the general HUI2 scale -0.83, on the “pain” scale -0.93, and on the “emotions” scale -0.88 [14].

More than 85% of patients with cystic fibrosis exhibit signs of malabsorption due to exocrine pancreatic insufficiency [3]. This causes fat malabsorption, which leads to multiple nutritional deficiencies in children with cystic fibrosis. This includes various fat-soluble vitamins. Studies in children with cystic fibrosis have shown biochemical vitamin E deficiency in 90–95% of cases [4,5,6]. In addition to vitamin E, there are other nutrients whose deficiency causes peripheral neuropathy, namely thiamine (vitamin B1), riboflavin (vitamin B2), pyridoxine (vitamin B6), vitamin B12, folic acid and copper [11]. In this study, we reported the incidence and pattern of peripheral neuropathy in patients with cystic fibrosis and the association of this incidence with serum micronutrient levels.

A generalized analysis of scientific foreign and domestic literature shows that this problem still has a number of complex unresolved issues. Integrating mental health screening, early detection of neurological disorders, and targeted treatment of patients with CF may reduce the mortality and morbidity observed in this disease.

An analysis of the studied scientific and medical literature, materials of state registration and accounting of research work has shown that numerous scientific studies are currently being conducted aimed at optimizing an integrated approach to the diagnosis and treatment of patients with cystic fibrosis.

The development of modern methods for diagnosing neurological disorders, treatment and prevention to reduce the severity and incidence of complications of cystic fibrosis is important.

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