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## **Historical and modern aspects of mucoviscidosis in Russia**

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**Article received: 14.07.2013, accepted for publication: 18.11.2013.**

*The article is dedicated to historical and modern trials in the sphere of mucoviscidosis in Russia, peculiarities of clinical manifestations, pathophysiological and pathomorphological disorders and of the disease course with the analysis of the first results of the register of patients in the Moscow region. The aggregate result of this evaluation is the survival rate in the Moscow region that has become almost equal to the one in the USA and Europe and is considerably higher than in the other regions of the Russian Federation. Such a result reflects many components of specialized care rendered to mucoviscidosis patients in the Moscow region: special centers for children and adults have been founded, patients are actively and regularly checked and may be examined in detail during each visit, while pharmacological support is up to world standards; this is not yet present or is developed insufficiently in many RF subjects. The article also dwells upon the genetic peculiarities of mucoviscidosis important both for diagnosing the disease (including neonatal screening) and creation of a panel for DNA-diagnostics and for determining the disease course to a considerable extent. It also presents information on the prospects of gene therapy development and the first results of clinical studies.*

**Keywords:** mucoviscidosis, history, genetics, spread, register, infection, complications.

Mucoviscidosis, or cystic fibrosis, is the most frequent hereditary monogenic disease among Caucasians, which may result in an early fatal outcome unless treated adequately.

Life expectancy and quality improvement is deemed a criterion of successful fight against mucoviscidosis. From 1991 to 2013, survival of patients with mucoviscidosis had increased from 13 to 39.7 years in Moscow and the Moscow region, from 10 to 16 years – in Russia in toto; this demonstrates success in treatment of this disease.

Mucoviscidosis (MV) is a pathology caused by mutation in gene *CFTR* (cystic fibrosis transmembrane conductance regulator) disturbing transport of chlorine, sodium and bicarbonate ions in epithelial cells; this results in progressive defect of endocrine glands of vital organs. Mucoviscidosis has been recognized as a multifactor and multisystem disease. At present, life expectancy of patients in the developed countries exceeded 45 years. The clinicians are more often encountering a range of new manifestations and complications, such as pancreatic diabetes, vasculitis, arthropathies, osteoporosis and reproductive disorders. Despite continuous improvement of treatment and rehabilitation of MV patients, survival rate has reached a plateau in the developed countries. Serious reconsideration of the situation established in regional centers, search for reserves of early disease diagnostics, prevention and timely therapy of pulmonary affection and organization of interdisciplinary approach to the problem are required.

Russian scientists and specialists made a historically determined contribution to MV research. Professors S.V. Rachinskiy and V.K. Tatochenko were the founders of the idea of serious research of this issue in the USSR; in 1967, they planned a PhD thesis subject –research of

spread, clinical-functional properties and peculiarities of MV course – for N.I. Kapranov. That research was successfully finished in 1970 and granted Maslov prize (USSR AMS).

Later, various studies were conducted not only in Moscow (at the USSR AMS research institute of pediatrics) and Leningrad (at the research institute of pulmonology under the direction of Professor T.E. Gembitskaya), but also in range of other large scientific center of Russia and union republics of the former USSR.

In 1974, the first monograph “Mucoviscidosis in children” (by S.V. Rachinskiy, V.K. Tatochenko and N.I. Kapranov) was issued in the Soviet Union.

In 1977, a joint (Soviet-Yugoslavian) monograph edited by Academician M.Y. Studenikin and Professor S. Silevic (SFRY) was issued; it presented peculiarities of bronchopulmonary system affection and a range of other vital organs and systems in children with MV.

In 1985, a monograph on MV was issued by N.I. Kapranov and S.V. Rachinskiy; it summarized many years of scientific research and clinical observations of a sufficiently large population of children with MV. In those same years, serious research of MV was successfully performed at the research institute of pediatrics (R.G. Artamonov, E.B. Bryum, B.A. Markov, O.F. Lukina, I.K. Volkov, V.I. Serbin, Z.M. Mikhaylova, R.A. Dobrovolskaya, E.V. Sereda, L.L. Nisevich et al.).

Later, issues of pathomorphological and pathophysiological peculiarities, microbiological status, immunological, microcirculatory and cardiovascular disorders at MV were studied in more detail (K.K. Primbetov, M.Y. Niyazova, A.B. Abilov, M.G. Georgobiani, I.E. Turina, L.A. Petrosyan). Serious research of affection of gastrointestinal tract and hepatobiliary system (N.Y. Kashirskaya) and of need in clinical-functional kinesitherapy efficacy as well (O.I. Simonova) ought to be mentioned especially.

The issue of MV in adults was being researched in almost the same years both in Saint Petersburg (T.E. Gembitskaya and her protégés L.A. Zhelenina, A.G. Chermenskiy, L. Kovalyova etc. and also V.S. Baranov, T.E. Ivachshenko etc.) and Moscow under the direction of Academician A.G. Chuchalin (L. Kronina, E.L. Amelina, S.A. Krasovskiy, V.A. Samoylenko, M.V. Samsonova, A.L. Chernyayev, A.V. Chernyak, S.N. Avdeev etc.).

Then, pulmonologists, gastroenterologists and geneticists started to study mucoviscidosis in other cities of Russia (E.A. Sirotkin, N.I. Romanenko, V.V. Chikunov, M.M. Chepurnaya, A.F. Neretina, D.F. Sergiyenko, E.T. Yagubyants, L.V. Ulyanova, M.A. Skachkova, E.N. Akhmadeyeva, I.K. Asherova, E.I. Kondratyeva, L.P. Nazarenko, O.N. Odinkova, T.V. Simanova, S.A. Shadrin etc.).

Genetic peculiarities of MV have been intensively studied in Russia since 1992 (E.K. Ginter, N.V. Petrova, V.S. Baranov, T.E. Ivachshenko, S.A. Krasovskiy, O.I. Golubtsova, S.L. Kozhevnikova, G.V. Pavlov etc.).

A network of 57 regional centers for diagnostics and treatment of children and of 10 centers for adult MV patients has been founded in Russia. Most are establishing registers including epidemiological properties, information on the main diagnostic criteria and the first disease symptoms, current parameters of nutritive and infectious status, pulmonary function parameters, frequency of exacerbations, complications and volume of baseline therapy.

A register of patients allows presenting the most significant symptoms of the disease. Apart from the traditional respiratory manifestations, malabsorption symptoms and malabsorption-associated low nutritive status, clinically significant symptoms are: chronic, especially polypous, rhinosinusites, rectal prolapse and electrolytic disorders in small children, which often manifest themselves with live-threatening reduction in levels of potassium, sodium and chlorides.

Active diagnostics, treatment, medical-social adaptation of MV patients are performed and public parental organizations involving both specialists and adult MV patients have been founded in regional centers.

MV spread in most countries of Europe and North America is 1:2,000-4,000 neonates. Lower frequency – 1:4,800-14,000 neonates – is observed in different regions of Russia; supposedly, due to blending of Slavic and Finno-Ugric populations during the formation of one Russian

people [1, 2]. It ought to be mentioned that mucoviscidosis had not been diagnosed in a significant number of patients until recently, and diagnosis would be established on late stages. Since introduction of MV to the compulsory neonatal screening program in 2007, considerable improvement of the disease diagnostics in Russia has been observed. Adequate therapy is prescribed earlier to their patients revealed in the process of neonatal screening than in the event of diagnostics based on clinical symptoms. Moreover, neonatal screening allows reducing delayed diagnosis-related stress for parents of ill children. Screening also presupposes possibility of early genetic consulting (before conceiving another child), which may influence reproductive behavior of couples and their relatives. Thus, MV rate among neonates reduced by 15-30% after introduction of a screening program in France (Province of Brittany). Introduction of neonatal screening in Russia (Moscow, Saint Petersburg, Voronezh, Kemerovo, Cheboksary, Yaroslavl etc.) facilitated early MV diagnostics: the number of patients with diagnosis established at an age of 0-12 months increased from 45 to 70%.

More than 11 mn neonates were examined in 2006-2013. MV morbidity in Russia is 1:19,498 neonates [1]. However, we believe that screening will inevitably lose its preventive meaning in the event of no general population coverage of neonates.

Mucoviscidosis is characterized by wide range of clinical manifestations, partially due to high rate of gene *CFTR* mutations (<http://www.genet.sickkids.on.ca/cftr/>), which affect the function of protein CFTR differently. Depending on the mechanism altering the function of protein CFTR, gene *CFTR* mutations are divided into 6 classes (tb.) [3]. Class I-III mutations alter the function of protein CFTR more severely than class IV-VI mutations; they are also associated with classic MV.

**Table 1.** Gene *CFTR* mutation classes

Class	Mutations	?
I	Protein synthesis disorder	G542X, W1282X, R553X, 621+1C>T, 2143delT, 1677delTA
II	Protein processing or transport disorder	F508del, N1303K, I507del, S549I, S549R
III	Regulation disorder	G551D, G1244E, S1255P
IV	Conductance reduction	R334W, R347P, R117H
V	Reduction in the level of normal protein or RNA proteins	3849+10kbC>T, A455E, IVS8(5T), 1811+1,6kbA>G
VI	Protein stability reduction	S1455X

2 class I, II or III mutations in homozygous and compound condition are always associated with pancreatic deficiency; these mutations are called severe with regard to pancreatic dysfunction. Patients with preserved residual pancreatic function have at least 1 class IV, V or VI mutation; these mutations are called mild, i.e. mild mutations dominate over severe with regard to pancreatic phenotype [4, 5].

It is well known that class I or II mutations in both chromosomes are associated with severer pulmonary affection and shorter life expectancy [1, 5, 6].

The spectrum and relative gene *CFTR* mutation rate has been studied in a broad sample of MV patients (776 patients) from different regions of Russia in a Moscow center. The following were considered diagnostically significant mutations: F508del (54.2%), CFTRdele2,3(21kb) (7.2%), 2143delT (2.1%), W1282X (2.0%), N1303K (1.9%), 3849+10kbC>T (1.9%), 2184insA (1.7%), G542X (1.3%), 1677delTA (0.8%), 3821delT (0.8%), R334W (0.7%), L138ins (0.6%) and 394delTT (0.5%). The share of unidentified mutations was 23%. Differences in mutation spectrums and disease rate complicate development MV DNA-diagnostics protocols and genetic consulting of population of various ethnic groups in different regions to a certain extent. Although variability of the MV clinical course is undoubtedly caused by multiplicity of genotypes, differences in the disease course in patients with the same mutations (particularly, in

sibs) indicate that the MV clinical presentation is affected by many factors: CFTR-mutations, modifying variants both in gene *CFTR* and other genes; environmental factors, including therapy, are also important [5, 7, 8].

At the age of 0-12 months of age or later, often – after a viral infection reducing efficacy of local antimicrobial protection mechanisms, lower respiratory tract segments are colonized by a big number of various pathogenic microbes [1, 9, 10].

Growth of bacteria in bronchial trees of MV patients induces a significant release of neutrophils; expression of anti-inflammatory cytokines IL1 $\beta$ , tumor necrosis factor  $\alpha$ , IL6 and IL 8 increases in response to the inflammation as well. As has recently been shown, transcription of anti-inflammatory cytokines is regulated by nuclear factor NF- $\kappa$ B and transcription factor of activator protein AR1. Increased expression of these cytokines is accompanied by reduction in expression of IL 10 – an anti-inflammatory factor [3, 11-25]. Hyperproduction of anti-inflammatory cytokines stimulates mobilization of neutrophils and their congestion in bronchopulmonary system. Derivatives of these dying neutrophils – elastase, protease, oxidases and cytokines – may directly destroy pulmonary structures by affecting elastin and structural proteins. Moreover, neutrophil elastase is a potential stimulator of IL 8 and bronchial secretion production. Progressive reduction in functional parameters of the respiratory function is a clinical manifestation of vicious circle obstruction – infection – inflammation – pulmonary tissue damage [1, 6, 26].

Pronounced inflammation is detected in as much as 1/3 of infants with MV. At present, high-resolution computed tomography is recognized as a more sensitive and accessible method of revealing such structural disorders in the event of MV as thickening of bronchial walls, cysts, bronchiectases and atelectases [1].

Management plan for MV patients presupposes active and regular medical check-ups, pharmaceutical support and medical rehabilitation measures involving modern technologies. Many MV patients may be managed outpatiently, without disturbing their regular lifestyle, in case medical process is properly organized.

Regular check-up by mucoviscidosis center specialists is necessary to control condition of MV patients, including neonates without clinical manifestations of the disease.

Antimicrobial therapy, replacement therapy with pancreatic drugs, exercise therapy (physio- and kinesitherapy), diet therapy, mucolytic and vitamin therapy and treatment of MV complications are necessary to treat MV patients.

Comparison of volume and character of baseline therapy with the European centers demonstrating higher survivability of patients allows revealing main tendencies and weak points in the MV treatment strategy. Coverage of patients with replacement therapy using pancreatic enzymes corresponds to the number of patients with exocrine pancreatic deficiency (92.7%). A significantly more frequent prescription of ursodeoxycholic acid (UDCA) is due to different prescription criteria. According to most international recommendations, UDCA is indicated in case 2 or more consequent transaminase increase episodes have been revealed [4, 5]. We tend to start prescribing the drug earlier, even if no clinical-laboratory symptoms of liver affection are present [9]. We deem such an approach justified as we did not notice transaminase level increase in some patients, even in patients with cirrhosis complicated by portal hypertension. Detection of the first ultrasonic symptoms of cholestasis, i.e. the increase in echogenicity of liver parenchyma, is an indication to prescribe UDCA [27, 28]. Despite the observed and described in literature reverse (due to the therapy) character of such alterations as fatty hepatosis and cholestasis, early prescription of UDCA did not result in reduction in the number of patients with liver cirrhosis in the population.

Use of inhalation anti-pseudomonas antibiotics does not correspond to the number of patients with the chronic infection caused by *Pseudomonas aeruginosa* and satisfies only 30-50% of the demand due to problems with regional pharmaceutical support. At the same time, antibacterial therapy strategy in respect of survivability of MV patients is of utmost importance; it requires concentration of effort of doctors and public organizations on this matter. Introduction of

subtherapeutic doses of macrolides into the baseline therapy, particularly, of azithromycin, is due to its anti-inflammatory and immunomodulating action. Its influence on the rate of exacerbations is well proven [7, 10]. Azithromycin (in intermittent mode) is recommended to all patients with chronic pseudomonas infection; however, wide use of azithromycin is restricted by low compliance due to the lack of fast and subjectively discernible effect.

Use of mucolytic drugs is aimed at dilution of viscous secretion and effective clearing of the bronchial tree off viscous sputum. Despite active practical use of traditional mucolytic drugs at MV (thiols, ambroxol hydrochloride, saline), the drug of choice is, without any doubt, a genetically engineered mucolytic dornase alfa (Pulmozyme, Hoffmann-La-Roche Ltd., Switzerland). The drug entered the list of drugs purchased for treatment of MV patients in the framework of program “7 nosologies” approved by the Decree of the Government of the Russian Federation of 2 October 2007. High percentage of use of the drug (89.5%) is connected with its financial availability at the expense of federal budget.

High clinical-functional efficacy and safety of dornase alfa was proved for patients of all age groups (from 1 month of age) and patients in severe condition, who may be prescribed to take the drug up to two times per day. According to foreign research, authors’ clinical observations and special studies, dornase alfa features important non-mucolytic effects and is also indicated to patients undergoing genetic therapy. Positive experience of using this drug in children of 2 months of age and older at the Russian MV center and a range of regional centers and the data presented in scientific publications allowed expanding age limits of dornase alfa use and apply the drug in the patients revealed in the process of neonatal screening [26]. Such a wide and early prescription of a genetically engineered mucolytic will allow evaluating efficacy of its long-term application in respect of regular pulmonary function reduction, prevention of pseudomonas infection colonization and reduction in the number of exacerbations.

Broncholytic drugs as part of the baseline therapy are represented in a far smaller number in comparison with European centers. Tactics of Russian specialists is based on the use of broncholytic spasmolytics only in the patients with reversible obstruction component or in those who experience subjective improvement of bronchial patency after inhalation of a short-acting  $\beta_2$ -agonist.

Microbiological flora character has changed significantly within the latest decade. The most widespread bacteria are *Staphylococcus aureus*, *Haemophilus influenzae* and *P. aeruginosa*. An increase in the number of patients infected with different gram-negative flora is being observed: *Stenotrophomonas maltophilia* (3%), *Acinetobacter* (1%), *Achromobacter* (*Alcaligenes*) *xylosoxidans* (2%), *Ralstonia pickettii* (1%), *Burkholderia cepacia* (4%), fungi, including *Aspergillus*, *Nontuberculous mycobacteria* etc.

The leading role in the structure of non-fermentative gram-negative microbes belongs to *P. aeruginosa*. Detection of other types of human non-pathogenic pseudomonades (*Pseudomonas putida* and *Pseudomonas fluorescens*) may be related to erroneous identification of other representatives of non-fermentative gram-negative flora, e.g., *A. xylosoxidans*. This requires regular quality control of regional laboratories and use of reference laboratories to avoid diagnostic errors. Up to 3 *P. aeruginosa* morphotypes differing in sensitivity to antibiotics may be identified in one sputum sample: planktonic, microcolonial and mucoid. Growth of antibacterial resistance is characteristic of the recent years. *Pseudomonas* drug resistance level depends on microbiological status of patients as well (primary plating or chronic infection). High sensitivity of strains at primary *P. aeruginosa* plating allows assuming colonization of external microbes to a high probability extent, whereas resistance of the chronically infected patients is in direct proportion to duration and volume of the conducted anti-pseudomonas therapy. Direct correlation of time of primary *P. aeruginosa* plating with attendance of childcare centers, frequency and duration of hospitalizations has been established; this allows making unambiguous conclusions with regard to toughening of indications for inpatient stay and upbringing of small children in organized groups of children. Direct correlation of resistant *P. aeruginosa* strains revealed in patients at primary plating with frequency and duration of

inpatient stay reaffirms the need in a better weighted approach to therapy of patients with *S. aureus* colonization and identification of indications to hospitalization. Resistance level is significantly higher and increases with time in the patients chronically infected with *P. aeruginosa*, apparently, due to massive and prolonged antibacterial therapy.

Infection with *B. cepacia* has become especially dangerous in recent years; it significantly aggravates patient's condition and prognosis. According to the data of FSI "Research institute of pulmonology" of the FMBA of Russia (Moscow), in 2009 *B. cepacia* was revealed in sputum of adult MV patients in 10.6% of cases, whereas in 2007 – only in 1.1% of all sputum samples [6]. Such a rapid growth was caused by admission of the already infected patients from pediatric clinics, cross infection among adult patients and spread of the infection in regional centers. According to the register of the adult patients observed at the Moscow MV center, in 2005-2010 *B. cepacia* was revealed in 44 (18.6%) out of 237 patients of 17-44 years of age altogether. Thus, the number of patients infected with *B. cepacia* is rapidly growing. Due to the spread of *B. cepacia*, hospitalization and outpatient treatment standards ought to be revised.

Among the non-fermentative gram-negative microbes, growth of *S. maltophilia* and *A. xylosoxidans* is being observed. The chronic infections associated with immune response to *S. maltophilia* is a predictor of more frequent exacerbations, although it does not cause any significant negative influence on pulmonary function [29, 30]. Spontaneous eradication is characteristic of *S. maltophilia*. Clinical strains of this type are specifically characterized by natural resistance to most modern wide spectrum antimicrobial drugs. Supposedly, MV patients are infected with unique *S. maltophilia* strains and their transfer from patient to patient is impossible [31]. However, we have been observing plating of *S. maltophilia* with similar antibacterial sensitivity in sibs for many years; this alone, without even molecular-genetic typing, questions this assertion.

*A. xylosoxidans* is characterized by difficulty of phenotyping; erroneous identification of other representatives of non-fermentative gram-negative flora, especially of *B. cepacia* complex, is often observed; this requires escalation of measures for control over the infection [32]. Chronic *A. xylosoxidans* colonization is accompanied by a pronounced inflammatory response and aggravation of clinical-functional indicators similar with such in the event of chronic pseudomonas infection. Failure of microbial eradication from the body in the setting of antimicrobial therapy is explained by their ability of form biofilm [8, 33]. Both microbes share high level of resistance to antibacterial drugs and detection after an intravenous anti-pseudomonas therapy course performed inpatiently.

The latter circumstance served as a cause of search for nosocomial sources of infection. Thus, e.g., a special examination was conducted at the Yaroslavl regional MV center, which showed that sink drains and toilets are an environment of non-fermentative gram-negative microbes. The same concerns equipment at the kinesitherapy room (high-frequency chest oscillation jacket) and hands of medical personnel. It is important that the washouts were sampled after the treatment of equipment in compliance with the SanRaN instructions and hand scrubbing with running water and soap. Detection of similar antibacterial sensitivity of the microbes identified in patients and washouts of the hospital equipment in 2 cases allows assuming possibility of hospital-acquired infection. Lack of molecular-genetic typing of causative agents does not allow deeming this assumption proven; nevertheless, it does not belittle need in toughening infectious control measures in respect of MV patients. Use of the exercise therapy room not only for joint, but also for individual exercises with MV patients without adequate treatment after each patient is inadmissible. Extrapulmonary percussion jackets must be individual. Detection of *S. maltophilia* and *A. xylosoxidans* in hospital sources and their identification in sputum after courses of antibacterial therapy against *P. aeruginosa* allows assuming nosocomial infection route and requires review of hygiene standards.

There is much information about significance of non-tuberculous mycobacteria for MV patients, whereas data on tuberculous infection at MV are extremely scarce. Moreover, there is an opinion that MV patients are resistant to tuberculosis due to the increased hyaluronic acid content in

bronchial mucous tunic in hetero- and homozygous MV gene carriers. At the same time, obvious tuberculosis development risk factors, primarily, altered mucociliary clearance, frequent need in intake of systemic corticosteroids, pancreatic diabetes and epidemiological situation in Russia forced us to attract more detailed attention to this issue. By way of polling the leading employees of Russian regional centers, we obtained information on the 8 more MV patients who had developed tuberculosis. It ought to be mentioned that in 4 cases the patients had obvious clinical symptoms of severe exacerbation; radiographic presentation was characterized by dissemination. Fatal outcome was observed in 2 cases. Mycobacteria were revealed as early as in the stage of autopsy with the help of a microscope. At the same time, we obtained information on the 3 MV patients who had developed tuberculosis from our French colleagues. Positive result of the anti-tuberculous therapy was achieved in all cases.

Summarizing the obtained data, it ought to be mentioned that the categories most vulnerable to tuberculosis are adolescents and young adult patients. The average age is  $18 \pm 5.5$  years. The determinative criterion in each case was the microbiological laboratory conclusion. A distinctive feature of Russian patients in comparison with French parents is multiresistance of strains of the revealed mycobacteria, supposedly, due to infection with bacilli of the patients who had undergone treatment with anti-tuberculous drugs. High spread of HIV-infection, large emigration flows and shortage of adequate treatment ought not to be disregarded. It may also be caused by long-term intake of antibacterial drugs featuring anti-tuberculous activity (aminoglycosides, fluoroquinolones). We concede the possibility of inadequate therapy of a latent tuberculous infection. It ought to be recognized that tuberculosis is actually not often encountered at MV; however, it may be a potentially dangerous complication, which is why disregarding bacteriological sputum study in respect of *M. tuberculosis* seems ill-considered, especially in adolescents from epidemiologically problem countries.

MV is a disease affecting bone stock mineralization processes. At present, vitamin D deficit in MV patients is corrected empirically at Russian centers, without considering its serum content; this renders its compensation and timely correction impossible. Another complication is that there are usually no specific clinical symptoms, even in the event of a pronounced deficit, whereas all international vitamin D dosage recommendations are based on its serum concentration. In routine practice, the starting points for dose selection are age and season unless daily vitamin D serum level monitoring is possible. The effort aimed at increasing bone stock mineral density is especially important for the process of growth – in childhood and adolescence. The approaches aimed at maximization of physical exercising and increase in the amount of consumed dairy products are rather reasonable. Evidently, despite the lack of clinical manifestations of pancreatic deficiency, MV patients require additional vitamin D dotation. Control of its serum level is required to specify intensity of the vitamin deficit. Hypogonadism and late puberty characterize MV patients; this is another bone mineral density reduction risk factor.

Introduction of bone densitometry in the patient examination algorithm from adolescence seems reasonable. Bone stock mineralization reduction may indicate severity of the disease course.

Gastrointestinal tract's alterations at MV are numerous. Exocrine pancreatic deficiency caused by the primary genetic defect is determinative from an early age. Organ's functional condition is evaluated on the basis of determination of pancreatic elastase-1 (E1) stool level. E1 stool content is less than 100 mcg/g in patients with pronounced pancreatic deficiency. There are no clinical symptoms of deficiency in pancreatic enzymes in case E1 level is over 200 mcg/g. In that case, patients are heterozygous in respect of mild mutations, such as 3849+10kbC>T, E92K, 3272-16T>A. This fact reconfirms phenotype correlation of the preserved pancreatic function with the certain genotype and allows orientating geneticists towards the search for certain mild mutations in case respiratory symptoms are prevalent to a high degree of probability. At the same time, such patients may still undergo slow development of chronic pancreatitis [8].

Frequency and severity of changes in liver of MV patients increase with life expectancy increase. Early diagnostics assumes special relevance, as there are data on reverse character of changes

(such as fatty hepatosis, cholestasis) under the influence of the therapy [34, 35]. According to different authors, multinodular liver cirrhosis develops in 5-20% of cases. The first symptoms of cholestatic changes (according to the ultrasonic examination) and exceeding of reference values of alkaline phosphatase are indications for its prescription. The most effective method of preventing bleeding of varix-dilated esophageal veins ligation; however, accessibility of this method for pediatric patients in Russia poses certain issues.

Mucoviscidosis was one of the first diseases to feature a developing genetic therapy. Complete replacement of a mutant gene with a normal copy is yet impossible; however, small molecules capable of modifying the mutant protein CFTR in a way that its function comes nearer to the normal state have been identified. Possibility of performing therapeutic measures with the measures determined by mutation class is a relevant subject for discussion. Efficacy evaluation of CFTR modulators is based on the identification of molecular capability of increasing amount of protein CFTR on the surface of epithelial cells and/or potentiating its function. It is possible to conduct pharmacological modeling of ionic transport using the so called correctors and potentiators [36, 37].

Molecules VX-809 and VX-661 are promising agents capable of correcting CFTR processing defect caused by mutation F508del [11-17]. Such a combination is reasonable and understandable: protein CFTR moves to the apical surface of the epithelial cell and is then activated by a potentiator. Drug VX-809 – a bioavailable F508del-corrector when taken *per os* – underwent the second stage of a placebo-controlled study in a group of patients homozygous in respect of mutation F508del. As a result, CFTR activity growth and reduction in sweat chlorides in a group taking the drug were demonstrated [13]. At present, combination of VX-809 and VX-661 with ivacaftor is studied among patients with mutation F508del [17-19].

Molecule PTC124 (ataluren) facilitating reading of the prematurely truncated codons in CFTR RNA is being actively researched at the moment. Results of a recent 12-week-long study of ataluren (PTC124) in 19 patients – carriers of at least 1 nonsense mutation – showed time-dependent increase in CFTR activity increase, improvement of clinical-functional parameters and high tolerance to the drug [20, 21]. The 3 stage of clinical research is in progress. CFTR is not the only channel of an epithelial cell responsible for maintaining level and composition of the epithelium-covering fluid. There are alternative chloric channels, including calcium-dependent and P2Y-receptor activated with adenosine triphosphate [21, 25].

2 drugs appeared in the field of view of researchers: denufosol, which stimulates chloride secretion [22-24] and lincovutide (Moli1901), which demonstrates improvement in the difference of nasal potentials at application on the nasal mucous tunic [3]. Apart from the correction of ionic transport defect by way of improving chloride secretion via Ca-activated chloric channels, denufosol inhibits sodium absorption affecting epithelial Na-channels and stimulates increase in the ciliary beating reduction. The studies that have been performed allow assuming that denufosol is capable of slowing down the pulmonary function reduction in MV patients. Clinical status and survivability improvement of MV patients also result from the development of therapeutic strategies based on understanding of MV molecular mechanism.

Thus, systemic exocrine dysfunction – result of *CFTR* gene mutations – leads to a multi-organ body affection, which requires interdisciplinary approach to the definition of tactics and strategy of patient treatment. Early diagnostics, efficient preventive measures aimed at maintaining nutritive and respiratory status, prevention of complications and control of respiratory tract's infectious process will allow reaching the life expectancy and quality level of MV patients achieved in the developed countries.

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