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THE MAIN PATHOGENETIC CONSTITUENTS OF COMORBID CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC PANCREATITIS (LITERATURE REVIEW)

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Key words: *chronic obstructive pulmonary disease, chronic pancreatitis, cystic fibrosis, cystic fibrosis transmembrane regulator protein, smoking.*

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Objective. *The main goal was to research data analysis of the literature on the influence of the state of CF gene (cystic fibrosis) in the course of comorbid chronic obstructive pulmonary disease and chronic pancreatitis.*

Conclusions: *The analysis of the data of the literature found increased frequency of heterozygous carriers of cystic fibrosis gene mutations among individuals with chronic pancreatitis and bronchopulmonary disorders such as bronchial asthma, bronchiectasis compared with the general population. Also found a negative effect of tobacco smoke on the function of the cystic fibrosis transmembrane regulator protein and as a result thickening secretions of exocrine glands.*

Ключевые слова*: хроническое обструктивное заболевание легких, хронический панкреатит, муковисцидоз, белок трансмембранного регулятора проводимости муковисцидоза, курения.*

Клиническая и экспериментальная патология Т.16, №2 (60). С.110-114.

ОСНОВНЫЕ ПАТОГЕНЕТИЧЕСКИЕ ЗВЕНЬЯ КОМОРБИДНОГО ТЕЧЕНИЯ ХРОНИЧЕСКОГО ОБСТРУКТИВНОГО ЗАБОЛЕВАНИЯ ЛЕГКИХ И ХРОНИЧЕСКОГО ПАНКРЕАТИТА (ОБЗОР ЛИТЕРАТУРЫ)

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Цель работы*: основная цель научного исследования заключалась в проведении углубленного анализа данных литературных источников о влиянии состояния гена МВ (муковисцидоза) на коморбидноє течение хронического обструктивного заболевания легких и хронического панкреатита.*

Выводы: *в результате проведенного анализа данных литературных источников обнаружено увеличение частоты гетерозиготного носительства мутаций гена муковисцидоза среди лиц с хроническим панкреатитом и патологией бронхолегочной системы, а именно больные бронхиальной астмой, бронхоэктатической болезни по сравнению с общей популяцией. Также обнаружен негативное влияние табачного дыма на функцию белка муковисцидозного трансмембранного регулятора что, проявляется сгущением секрета экзокринных желез.*

Ключові слова*: хронічне обструктивне захворювання легень, хронічний панкреатит, муковісцидоз, білок трансмембранного регулятора провідності муковісцидозу,*

ОСНОВНІ ПАТОГЕНЕТИЧНІ ЛАНКИ КОМОРБІДНОГО ПЕРЕБІГУ ХРОНІЧНОГО ОБСТРУКТИВНОГО ЗАХВОРЮВАННЯ ЛЕГЕНЬ ТА ХРОНІЧНОГО ПАНКРЕАТИТУ (ОГЛЯД ЛІТЕРАТУРИ).

О.С. Хухліна, О.О. Урсул, О.С. Воєвідка, Л.В. Каньовська, В.С Гайдичук, О.В. Андрусяк

Мета роботи*: основна мета наукового дослідження полягала у проведені поглибленого аналізу даних літературних джерел щодо впливу стану гена МВ (муковісцидозу) на коморбідний перебіг хронічного обструктивного захворювання легень та хронічного панкреатиту.*

Висновки*: в результаті проведеного аналізу даних літературних джерел встановлено збільшення частоти гетерозиготного носійства мутацій гена муковісцидозу серед осіб із хронічним панкреатитом та патологією бронхолегеневої системи, а саме хворі на бронхіальну астму, бронхоектатичну хворобу у*

куріння.

порівнянні із загальною популяцією. Також виявлений негативний вплив тютюнового диму на функцію білка муковісцидозного трансмембранного регулятора, що проявляється згущенням секрету екзокринних залоз.

Клінічна та експериментальна патологія Т.16, №2 (60). С.110-114.

In recent years scientists from different countries state an increased part of patients with comorbid pathology [6]. In case of comorbid pathology prediction and degree of severity of the underlying pathology becomes worse [1]. Nowadays much attention is paid to the main pathogenetic constituents of chronic obstructive pulmonary disease (COPD), as adult able-to-work individuals are afflicted most frequently resulting in considerable social-economical problems [10]. COPD remains to be one of the leading causes of sickness and mortality in the world [4]. According to the WHO expert estimation mortality rate due to COPD will stand third among the main causes of death up to 2020. Till 2009 COPD sickness rate was not registered as a separate index in medical reports in Ukraine, although since that time 377 000 cases of COPD have been registered, and only in 2010 there were about 420 000 cases registered. In 2011 occurrence of COPD was no less than 3,5-4,2% of the adult population in our country [4].

In clinical practical work a frequent association of COPD with digestive pathology is found, especially with chronic pancreatitis (CP) [2]. The occurrence of CP in Europe is 25-26,4 cases per 100 000 of population, in Russia - 27,4-50,0 cases per 100 000 of population [8]. According to the data of the studies carried out in Ukraine the rate of CP sickness in 2012 was 226 cases per 100 000 population, occurrence - 2471 per 100 000 of the population [11]. In recent 30 years more than twice increase of sickness rate of acute and chronic pancreatitis has been observed [8]. A common risk factor of COPD development is long smoking (60-cigarettes-a-day smokers) promoting maintenance of chronic inflammatory response in patients with respiratory pathology [10]. In 2015 the Centre of Control and Prevention of Diseases in the USA estimated 15,1% smokers among adult population (36,5 million of people), every day more than 3 200 people under 18 years of age smoke their first cigarette, 2 100 among them become smokers. Smoking causes approximately 443 000 deaths annually. In Russia 43,9 million of adult population smoke (60,2% of men, and 21,7% of women) [9]. According to the information provided by the Ministry of Public Health of Ukraine in 2012 the number of smokers under the age of 18 was 8,6 million. In western and southern regions of Ukraine 63% of the whole population smoke (45% of men and 8% of women). By the year of 2025 this number is expected to be increased to 500 million of women (about 20% of the whole female population) [5]. Nowadays a considerable part of the population is exposed to passive smoking, which is a substantial problem concerning the spread of sickness not only among adult population but among children as well [9].

Researchers from many countries have found the correlation between the effect of genetic, ecological factors and development of diseases [3,31,41]. In 1989 cystic fibrosis gene mutation was identified and the carriers of cystic fibrosis (CF) gene mutation were found to be susceptible to the development of lung pathology [34]. CF gene mutation occurs in patients with congenital bilateral absence of the seminiferous ducts [24], bronchial-pulmonary aspergillosis [14], chronic sinusitis [28], idiopathic bronchiectasis [16,46]. Chronic pancreatitis (CP) is of a hereditary etiology from 5 to 10 % of cases [39]. In patients with idiopathic pancreatitis mutation of the gene coding cation trypsinogen (PRSS 1) [35] is found in 52 % of cases, in 20-23 % mutation of the gene coding trypsin pancreatic secretory inhibitor (SPINK 1) is found [43], and in 13,4-25,9 % cystic fibrosis gene mutations are found (cystic fibrosis transmembrane regulator - CFTR) [13].

Cystic fibrosis is a hereditary disease with autosomal-recessive type of inheriting characterized by CF gene mutation resulting in changes of the protein structure of CF transmembrane conductivity regulator (CFTCR) functioning as цАМФ-dependent ion channels responsible for the transport of chlorine and sodium ions, and located on the apical surface of the epithelial cells (lungs, liver, intestine, pancreas, sweat glands, reproductive organs) [17,39,42]. Ion channels regulating transport of sodium and chlorine ions provide appropriate hydration and ion content of bronchial secretion [44]. CF remains one of the leading causes of sickness and mortality in the world at the expense of progressing reduction of the lung function and in 85% of cases development of insufficient exocrine function of the pancreas, irrespective of a contemporary level of development of therapeutic possibilities [20, 22, 25]. Nowadays more than 1800 mutations of CF gene are known [29]. The following occurrence of CF gene mutations is detected: ΔF508 (53,2%), CFTR dele 2,3 (21kb) (5,5%), N1303K (2,7%), 2184insA (2%), 2143delT (2%), W128 2X (1,8%), G542X (1,7%), 3849+10kbCT (1,7%), R334W (0,8%), S1196X (0,6%) [12]. Occurrence of CF is of a high frequency among the population in the Caucasus (1:2500) [38]. The risk of carriage of CF gene mutations varies depending on ethnic belonging with a higher degree of occurrence among people of the northern European origin (1/25), Ashkenazi Jew descendants (1/29) [20]. In the United State the number of people being carriers of CF gene mutations is the following: 1:29 among Caucasus Americans, 1:46 among Spanish Americans, 1:65 among African Americans and 1:90 among Asian Americans [29]. According to the results of 10-year studies (since 1996 till 2006), conducted among healthy adult Italian population (77,9% of all the examined individuals were from Venetian region), where among 59,782 individuals without any clinical or familial signs of CF the frequency of carriage of CF gene mutation was found to be 1:31. When the study included individuals with familial anamnesis of CF sickness the frequency of

CF gene mutation increased to 1:25 [20].

In Ukraine on the basis of testing of 720 healthy individuals the frequency of heterozygous carriage of CF gene mutations was found to be 1: 29, and CF frequency was 1 : 3 3000 of newborns [7,15]. Considering the data obtained concerning the frequency of heterozygous carriage of CF gene mutations and rates of annual birth rate (509,000 newborns), the researchers concluded that expected annual birth rate of children with CF is about 143 children [15].

A great number of phenotypic manifestations of CF gene mutations are described ranging from mild pulmonary diseases with sufficient function of the pancreas to severe lung pathology with insufficient function of the pancreas. Individuals with heterozygous condition of CF gene do not present any clinical signs of CF [29]. Due to a high frequency of CF gene mutations in 2001 American College of Medical Genetics and American College of Obstetrics and Gynecology published instructions concerning screening of the population with CF. certain recommendations were suggested for family couples from high risk groups who were planning children [36,48].

The data of literature concerning the effect of mild CF gene mutations on comorbid course of COPD and CP are rather disputable. Investigations of foreign researchers are indicative of the fact that frequency of heterozygous carriage of CF gene mutations is rather high among individuals with COPD as compared to the general population [35]. Persons with heterozygous condition of CF gene have lower indices of FEV1 as compared to the general population [33]. A negative effect of tobacco smoke is described on ion transport in the epithelial tissue of the trachea of dogs, and revealed pathological changes were suggested to be in the basis of abnormal mucocilliary cleaning of the respiratory tract of smokers [23]. The studies concerning the effect of tobacco smoke on the epithelium of the human respiratory tract found that the function of CFTCR protein decreases under the effect of smoking resulting in thickening of bronchial secretion and disorders in the cleaning mechanism of the respiratory tract [18, 21,25,35]. Preliminary studies have found restoration of function of CFTCR protein in the epithelium of the nasal passages after elimination of smoking during one year, while in the pulmonary tissue these processes can last longer [13,25]. These and other conceptions require further investigations. Hypoxia also can promote inhibition of the function of CFTCR protein [45].

During the recent years a clear connection between CF gene mutations and development of chronic pancreatitis has been found [27,32]. Reduced function of CFTCR protein in the epithelial cells of the pancreatic ducts is manifested in certain patients with idiopathic CP [47]. Susceptibility of the pancreas to internal obstruction of ducts due to dysfunction of CFTCR protein results in a high concentration of macromolecules in secretion and reduction of liquid component. This pathogenetic mechanism in patients with idiopathic CP is associated with CF gene mutations and differs from other pathogenetic mechanisms in case of different types of CP, when acinous cells are afflicted first of all [26]. The frequency of heterozygous carriage of CF gene mutations among patients with CP is higher as compared to the general population [40].

The fact of participation of CFTCR protein in penetration of glutathione through the cellular membrane remains rather interesting [30]. Glutathione is an important tripeptide (glutamile, cysteine, glycine) containing sulfhydryl group enabling it to protect cells against active forms of oxygen, electrophilic compounds and xenobiotics. Dysfunction of CFTCR protein accompanied by disorders of glutathione penetration through the epithelial membrane can contribute into intensification of oxidative stress [17].

Higher occurrence of CF gene mutations are found among the patients with bronchial asthma as compared to the general population [19,37].

Therefore, the role of genes able to effect the development and progress of comorbid course of COPD and CP is rather disputable and requires further studies in this direction with the aim to improve treatment of this category of patients.

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