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Genetic Predisposition of Chronic Obstructive Pulmonary Disease in Extremely Cold Climate

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ABSTRACT

This article reflects the genetic aspects of chronic obstructive pulmonary disease. Modern molecular biology concept comes from an imbalance in the system proteolysis - antiproteoliz , alpha 1- antitrypsin is a major inhibitor of serine proteases, which include trypsin, chymotrypsin, neutrophil elastase, tissue kallikrin, Factor X "a" and plasminogen. The gene PI (proteinase inhibitor) located on the long arm of chromosome 14 (14q31- 32), and the gene product is glycoprotein alpha$_1$ - antitryprisin. Two types of cells expressing the gene PI - macrophages and hepatocytes, the function of hepatocyte, associate tissue specificity of the inhibitor.

Keywords: chronic obstructive pulmonary disease, alpha$_1$ - antitrypsin.

Chronic obstructive pulmonary disease (COPD) develops when failure alpha$_1$ - antitrypsin based on etiopathogenesis lie mutations in genes CF (cystic fibrosis) and PI (protease inhibitor) [6].

There are several local defense units of bronchopulmonary system: mucociliary apparatus, ciliated cells and rheological properties of mucus humoral - immunoglobulins, lysozyme, lactoferrin, antiprotease, complement components, interferon, a cellular link, including alveolar macrophages (AM), neutrophils and lymphocytes; bronhoassociated lymphoid tissue (BALT) [1]. Based on the analysis of molecular and cellular changes in the respiratory tract of patients with COPD can be divided into four main stages of the disease:

1. Stage of aseptic inflammation. It is caused by excessive production of ROS and nitric oxide in the respiratory organs. Its main clinical manifestation is a productive cough. Significant biomarkers of this stage of COB are: increase in blood chemiluminescence of leukocytes and bronchoalveolar lavage of smokers and patients with increased concentration of nitric oxide in exhaled air in non-smoking patients.

2. Stage of obstructive changes. Its reason - the relative lack of otsantitripsin arising due to an imbalance of proteolytic enzymes and their inhibitors in lung tissue. Criterion is the degree of decrease in expiratory flow rate and elevated levels in the urine of patients' oksiprilin. It is also found increased content of hydrogen peroxide in the exhaled air.

3. Stage of reducing germicidal protection. It arises as a result of the blockade of oxygen-dependent bactericidal system of alveolar macrophages and neutrophils on the background of the development of atrophic changes in the bronchial mucosa. Method of estimating the degree of suppression of lung antibacterial protection needs to be improved. For this purpose it may be used to determine the degree of neutrophil myeloperoxidase oppressing blood or bronchoalveolar lavage, or the degree of suppression of production of ROS by neutrophils and macrophages. Clinical sign of this stage is the appearance of purulent sputum.

4. Stage of severe respiratory failure. The final stage of the development of chronic obstructive bronchitis caused by two reasons: a decrease in total respiratory alveolar surface due to emphysema and exhale collaboration of bronchioles due to atrophy of the elastic fibers and smooth muscle of their walls. Leading sign - hypoxemia. It is characterized as tense, but little effective work of external respiration [2].

In the 60s gene alpha$_1$- antitrypsin (α_1 -AT) was discovered and till this day it is continued to search for new genes. Laurell and Ericsson found that patients with low levels of alpha$_1$ - globulin serum revealed a high incidence of pulmonary emphysema, i.e., chronic obstructive pulmonary disease. Genetic polymorphism of α_1 -AT is not confined to a mutation leading to a decrease in the level of α_1 -AT in the serum. Currently, described a series of mutations, accompanied by a decrease in functional activity of the inhibitor. However, such cases are rare, and they can be linked only a small percentage of individuals predisposed to the development of COPD [5]. Also has been described principally new mutation in the gene α_1 -AT in 3 ' flanking area which has no relation to the amino acid sequence and therefore does not lead to amino acid substitutions in the molecule α_1 -AT, does not alter its physic -chemical properties. Theoretically, such a mutation should not have any clinical consequences. Nevertheless, a clear connection has been found this mutation (even in the heterozygous state) with susceptibility to COPD and bronchoecstasies. This mutation was discovered by two independent groups of researchers and it was not so rare - 15-20% of patients with emphysema and bronchoecstasies (in the control group of healthy individuals - not more than 5 %). Almost the same frequency was detected E.I. Samilchuk et al. (1997) in the Russian population [3]. This is most likely due to the fact that a mutation in the 3' -flanking region of the regulation of gene expression gives α_1 -AT. It is known that α_1 -AT relates to proteins known as "acute phase ", and its concentration in serum is increased in inflammatory processes 2-3. Such an increase in the concentration of α_1 -AT has a large biological sense, since to prevent tissue damage by proteolytic enzymes in the field of acute inflammation. Lack of acute phase increase in the level α_1 -AT in viral and

bacterial respiratory infections may contribute to tissue damage in neutrophil elastase and other proteolytic enzymes. At present the first results, which reveal the specific molecular mechanisms by the 3'- mutation which disrupts acute phase response. In the 90s drew attention to the gene encoding the alpha 1- antichymotrypsin (Samilchuk E.I., 1997) [3]. This inhibitor is also included in the group of serine; its gene is located in chromosome 14, in the same plot as its related gene PI.

Currently there are 75 known alleles of PI gene. They are divided into four groups: normal, they are characterized by physiological concentrations of serum alpha-1 - antitrypsin; scarce - the concentration of inhibitor reduced by at least 65 % of the norm, the "zero» – in a serum not detected and finally in serum normal level of inhibitor is registered, but its activity against elastase is reduced. PI- allele nomenclature is based on the electrophoretic mobility of glycoprotein - alpha1 - antitrypsin, option "A" is closest to the anode, the most popular variant "M" and a cathode - labeled «Z». The main shares of the gene pool (over 95 %) are three subtypes of the normal allele "M": M1, M2, and M3. Human pathology, of associated gene PI, falls on deficit and zero alleles. The main clinical manifestations of deficiency of alpha1 - antitrypsin are emphysema and juvenile cirrhosis. Delineated genetic emphysema cases , sometimes it is referred to as Essential , falls on a young age ; this form is often associated with cirrhosis [5].

However, there are described cases when in the elderly type ZZ was detected at moderate forms of emphysema. Revised data for the epidemiological study of genetic predisposition to emphysema suggest that in patients with chronic obstructive pulmonary disease, it is about 2 to 5%. The main pathogenetic mechanism that underlies the pathological process of low - inhibitory activity in lung neutrophil elastase structures, which leads to proteolytic degradation of respiratory tissue and primarily elastic fibers [3, 5].

Yakutia is the pole of cold, and clinical COPD picture proceeds more difficult than in other regions of the Russian Federation and the world in general. As a result of simultaneous clinical and instrumental studies in 2856 and residents of Yakutsk village Churapcha, proportion of COPD in the city was 14.1 % in rural areas - 20.5%. One of the main reasons for this is a significant prevalence of tobacco smoking among urban and rural residents especially Yakutia. The incidence of COPD among males over 60 years higher than that of women, it is almost 2 times in rural areas are 7.1 and 3.3 %, and in the ratio of men and women were about equal in city. According to our data, the frequency of colds was in 54.5% in city, and in rural areas - 43.9

%, which also explains the severe climatic conditions and is one of the risk factors for COPD. In this study, we noted that the disease is hereditary [4].

In the near future as a result of the research will be first identified genes for COPD in the Yakut population , will generate new data on chronic and COPD , the ways of transmission and prevention methods have been developed . The results can be used to improve the diagnosis, prevention and treatment of chronic human diseases associated with respiratory tract infection in extremely cold climates. A large number of gene mutations described COPD may cause a variety of clinical manifestations. Among those older than 40 years, the most frequent form with a primary lesion of the bronchopulmonary system, this determines the course and prognosis of the disease.

REFERENCES

1. Dvoretskiy L. I., Yakovlev S. V. Pozhiloy bol'noy i infektsiya [Elderly patients and infection]: rukovodstvo dlya vrachey [a guide for physicians]. Moskva: GEOTAR-Media, 2008, p. 362.

2. Mironova G.Ye., Vasilyev Ye.P., Velichkovskiy B.T. Khronicheskiy obstruktivnyy bronkhit v usloviyakh Kraynego Severa (Znacheniye antioksidantnogo statusa i antioksidantnoy terapii) [Chronic obstructive bronchitis in the Far North (The antioxidant status and antioxidant therapy)]. Krasnoyarsk, 2003, p. 169.

3. Samilchuk Ye. I. Rol' nasledstvennykh faktorov v razvitii khronicheskikh obstruktivnykh zabolevaniy organov dykhaniya [Role of hereditary factors in the development of chronic obstructive respiratory diseases]. Avtoreferat dissertatsii na soiskaniye doktora med. Nauk [Dissertation author's abstract on competition of Dr. med. Sciences], 1997.

4. Sivtseva A.I. [et al.] Khronicheskaya obstruktivnaya bolezn' legkikh v Respublike Sakha (Yakutiya) [Chronic obstructive pulmonary disease in the Republic of Sakha (Yakutia)]. Yakutsk, NEFU , el. version, 2013, p. 208.

5. Chuchalin A.G. Khronicheskiye obstruktivnyye bolezni legkikh [Chronic obstructive pulmonary disease]. Moscow.: ZAO Binom, 2000, p. 510.

6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: NHLBI/WHO workshop report, NIH publication. Updated July, 2013.

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