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ALPHA-1 ANTITRYPSIN DEFICIENCY AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstrakt

Introduction. Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder that manifests as pulmonary emphysema, liver cirrhosis and, rarely, as the skin disease panniculitis, and is characterized by low serum levels of AAT, the main protease inhibitor (PI) in human serum. The prevalence in Western Europe and in the USA is estimated at approximately 1 in 2,500 and 1 : 5,000 newborns, and is highly dependent on the Scandinavian descent within the population.

Chronic obstructive pulmonary disease (COPD) is one of the most essential causes of morbidity and mortality. In 2008, COPD was the fourth leading cause of death in the world, but the number of patients is still increasing and the World Health Organization (WHO) predicts that COPD will get the third most common cause of mortality in 2030.

The Aim. To acquaint the students and specialists of practical healthcare with a genetic disease, deficiency of alpha-1-antitrypsin

Methods. The study of publications on this subject included in the evidentiary basis the Cochrane Library EMBASE and MEDLINE, databases during the last 30 years.

Results. The most common deficiency alleles in North Europe are PI Z and PI S, and the majority of individuals with severe AATD are PI type ZZ. Type ZZ and SZ AATD are risk factors for the development of respiratory symptoms (dyspnoea, coughing), early onset emphysema, and airflow obstruction early in adult life. Environmental factors such as cigarette smoking, and dust exposure are additional risk factors and have been associated to an accelerated progression of this condition. AATD is caused by mutations in the SERPINA 1 gene encoding AAT, and is inherited as an autosomal recessive trait. The diagnosis can be established by detection of low serum levels of AAT and isoelectric focusing, PCR. For treatment of lung disease, intravenous alpha-1-antitrypsin augmentation therapy, annual flu vaccination and a pneumococcal vaccine every 5 years are recommended. Relief of breathlessness may be obtained with long-acting bronchodilators and inhaled corticosteroids. The end-stage lung disease can be treated by organ transplantation.

Conclusions. Preventive measures, such as smoking cessation, avoiding contact with pollutants, vaccine prevention of infections are measures that reduce the rate of progression of the disease. It is advisable to pre-clinical diagnostic of alpha1-antitrypsin deficiency that could determine the choice of occupation, place of residence, the lifestyle of an individual.

Keywords: alpha-1 antitrypsin, alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease, genetics, diagnostics.

Резюме

ДЕФИЦИТ АЛЬФА-1 - АНТИТРИПСИНА И ХРОНИЧЕСКАЯ ОБСТРУКТИВНАЯ БОЛЕЗНЬ ЛЕГКИХ

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Введение. Дефицит альфа-1 - антитрипсина (ДААТ) является генетическим заболеванием, проявляется эмфиземой, циррозом печени и в редких случаях как панникулит и характеризуется низким уровнем ААТ в сыворотке, который является основным ингибитором протеазы в сыворотке человека (PI). Распространенность в Западной Европе и в США оценивается примерно в 1: 2500 и 1: 5000 новорожденных, а в значительной степени зависит от скандинавского происхождения населения.

Хроническая обструктивная болезнь легких (ХОБЛ) является одним из наиболее важных причин заболеваемости и смертности. В 2008 году ХОБЛ была по значимости четвертой причиной смерти в мире, но количество больных продолжает расти и Всемирная организация здравоохранения (ВОЗ) прогнозирует, что ХОБЛ будет на третьем месте по наиболее распространенной причиной смертности в 2030 году.

Цель. Ознакомить студентов и специалистов практического здравоохранения с генетическим заболеванием, дефицитом альфа-1-антитрипсина.

Методы. Изучение публикаций по данной теме, вошедших в доказательную базу Кокрановской библиотеки, базы данных EMBASE и MEDLINE. Глубина поиска составляла 30 лет.

Результаты. Наиболее распространенные аллели дефицита в Северной Европе PIZ и PIS, и большинство людей с тяжелым ДААТ типа PIZZ. ДААТ ZZ и SZ являются факторами риска развития респираторных симптомов (одышки, кашля), раннего начало эмфиземы и обструкции дыхательных путей у взрослых. Экологические факторы, такие как курение, и воздействие пыли являются дополнительными факторами риска и связаны с ускорением прогрессирования данного заболевания. ДААТ вызывается мутациями в гене SERPINA1 кодирующих ААТ, и наследуется по аутосомно-рецессивному признаку. Диагноз может быть установлен при обнаружении низкого уровня сывороточного ААТ и методами ПЦР и изоэлектрофокусирования. Для лечения болезни легких внутривенно вводят заместительную терапию альфа1-антитрипсином, рекомендуется ежегодная вакцинация против гриппа и пневмококковая вакцина, каждые 5 лет. Одышка уменьшается назначением бронходилататоров длительного действия и ингаляционных кортикостреоидов. Трансплантация легких применяется в конечной стадии заболевания.

Выводы. Профилактические мероприятия, такие как отказ от курения, исключение контактов с поллютантами, вакцинопрофилактика инфекции являются мерами, уменьшающими темпы прогрессирования заболевания. Желательна доклиническая диагностика серпинопатии, что могло бы определять выбор профессии, место жительства, образ жизни индивидуума.

Ключевые слова: альфа-1-антитрипсина, дефицит альфа-1-антитрипсина, хроническая обструктивная болезнь легких, генетика, диагностика.

Түйіндеме

АЛЬФА-1 - АНТИТРИПСИН ТАПШЫЛЫҒЫ ЖӘНЕ ӨКПЕНІҢ СОЗЫЛМАЛЫ ОБСТРУКТИВТІ АУРУЫ

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Кіріспе. Альфа-1-антитрипсин тапшылығы (ААТТ) генетикалық ауру болып табылады, өкпе эмфиземасы, бауыр циррозы, панникулит түрінде байқалады және сарысудағыпротеаз ингибиторы болып саналатын ААТ деңгейінің төмендеуімен сипатталады. Батыс Еуропада және АҚШ-та аурудың таралуы шамамен 1: 2500 и 1: 5000 жаңа туған нәрестеге бағаланады және көбінесе скандинавиядан шығу тегімен байланысты.

Өкпенің созылмалы обструктивті ауруы (ӨСОА) аурушаңдық пен өлім-жітімнің маңызды себебі болып табылады. 2008 жылы ӨСОА әлемде өлім-жітімнің төртінші себебі болды, бірақ

науқастар саны өсуде, Дүниежүзілік денсаулық сақтау ұйымының (ДДҰ) болжамы бойынша, 2030 жылы ӨСОА өлім-жітімнің үшінші себебі болады деп күтілуде.

Мақсаты. Студенттер мен практикалық денсаулық сақтау мамандары осы генетикалық альфа1-антитрипсин тапшылығымен таныстыру.

Әдістер. Бұл жұмыстың дәлелдемелер базасы Кокрандық кітапхананың, EMBASE және MEDLINE мәліметтер базасына осы тақырып бойынша жарияланымдар зерттеу болып табылады. Іздеу тереңдігі 30 жыл.

Нәтижелері. Солтүстік Еуропада барынша кең таралған PI Z және PI S аллельдері және көптеген адамдарда ауыр AATT PI ZZ түрі байқалады. ZZ және SZ AATT респираторлық белгі (ентігу, жөтел), ересектереде эмфиземаның, тыныс жолдары обструкциясының ерте дамуының қатер факторлары болып табылады. Шылым шегу, және шаң-тозаң сияқты қоршаған орта факторлары қосымша қатер факторлары болып табылады және аурудың үдеуіне үлес қосады. AATT AAT кодтайтын SERPINA 1 гендегі мутациянәтижесінде туындайды және аутосомды-рецессивті белгі бойынша беріледі. Диагноз сарысудағы AAT төмен деңгейі және изоэлектрлік фокустеу, ПТР әдісі бойынша анықталады. Өкпе ауруларын көктамырішілік альфа1-антитрипсинмен орнын толтыру емін жүргізу арқылыемдеуді және әрбір 5 жыл сайын пневмококк қарсы вакцина, жыл сайын тұмауға қарсы вакцина егуді ұсынады. Ентігуді бәсеңдету ұзақ әсер ететін бронх кеңейткіштері және ингаляциялық кортикостероидтар арқылы жүзеге асады. Өкпе трансплантациясы аурудың соңғы сатысында қолданылады.

Қорытынды. Шылым шегуден бас тарту, поллютанттармен байланысты болдырмау, алдын-ала вакцина егу ауру үдеуін баялатудың шаралары болып табылады.

Альфа-1-антитрипсин тапшылығының клиникаға дейінгі нақтамалауы адамның кәсіп, тұрғылықты жері, өмір салтын таңдауын анықтайды.

Негізгі сөздер: альфа-1-антитрипсин, альфа-1-антитрипсин тапшылығы, өкпенің созылмалы обструктивті ауруы, генетика, диагностика.

Библиографическая ссылка:

Жумагалиева А. Н. Санитарно-эпидемиологическая характеристика медицинских отходов лечебно-профилактических учреждений города Семей / / Наука и Здравоохранение. 2016. №1. С. 127-131.

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Жұмағалиева А. Н. Альфа-1 - Антитрипсин тапшылығы және өкпенің созылмалы обструктивті ауруы / / Ғылым және Денсаулық сақтау. 2016. №1. Б. 127-131.

Chronic obstructive pulmonary disease.

Hundreds of millions worldwide suffer from asthma and chronic obstructive pulmonary disease (COPD) alone [6, 58]. One half of those who die prematurely from non-communicable diseases are in their productive years and the social costs and economic consequences in terms of lost productivity are considerable [67]. In 2010, COPD alone was estimated to have cost the global economy $400 billion [33].

In Kazakhstan, the number of patients with COPD has increased more than twofold in the last 10 years, constituting 321patients out of 100 thousand people in 2011. To compare, one of the most common diseases, diabetes is found 158.3 people per 100 thousand [38].

Chronic obstructive pulmonary disease (COPD) is defined as airflow obstruction that is not fully reversible. It results from abnormal inflammation following exposure to noxious particles or gases [48]. This is typically exposure to cigarette smoke but may also include exposure to biomass fuels and some industrial dusts. COPD clusters within families, suggesting that heritable factors play a role in the pathogenesis of this disease [1, 57]. The only genetic factor that is widely accepted to be associated with COPD is severe deficiency of α_1-antitrypsin [32, 42].

Objective. Conducting a search of literature on the study of the pathogenesis, clinical manifestations, epidemiology and treatment of

alpha1-antitrypsin deficiency in patients with chronic obstructive pulmonary disease

Methods. To achieve this goal was performed a systematic search of literature in the online resource. Were found 300 sources, including for analysis were selected – 68. Key points of forming search queries for the formation of the literature review were presented to the following elements: “alpha1-antitrypsin”, "alpha1-antitrypsin deficiency", "genetics", "chronic obstructive pulmonary disease".

Criteria for inclusion in the review of publications:

• Publications in the last 30 years;

• Publications indexed in the MEDLINE database, EMBASE;

• Publications with clearly formulated and statistically proven conclusions.

• Publications in English languages;

Exclusion criteria in the review of publications:

• Newspaper publications;

• unpublished observations;

• Summary reports.

Results and discussion

Structure and function of α_1 - antitrypsin

Alpha 1 - Antitrypsin (AAT) is a 52-kDa glycoprotein produced by hepatocytes and, to a lesser extent, by mononuclear monocytes whose main role is to effectively inhibit neutrophil elastase [13]. It is synthesised by hepatocytes [14, 28] and secreted into the plasma at a concentration of 1.9–3.5 mg/ml.It is also synthesised by and secreted from macrophages [13] and intestinal [36] and bronchial epithelial cells [16, 45]. The protein was initially named because of its ability to inhibit pancreatic trypsin [54]. Subsequently it has been detected to be an effective inhibitor of a variety of other proteinases including neutrophil elastase, [49] cathepsin G, [52] and proteinase 3 [26]. The broad spectrum of proteinase inhibition gave increase to its alternative name of α1-proteinase inhibitor, [26] although this too is inaccurate as other proteins in the α1 band of serum (such as α1-antichymotrypsin) are also proteinase inhibitors. Crystal structures have shown that AAT is composed of three β-sheets (A–C) and an exposed mobile reactive loop that presents a peptide sequence as a pseudosubstrate for thetarget proteinase [39,50]. The AAT gene spans 12.2 kb in length and has three non-coding (IA, IB, IC) and four coding (II, III, IV, V) exons; exon V includes the sequence coding for the reactive site of the AAT protein (Met358–Ser359). There is a close genetic linkage between the AAT and AACT genes, and it is likely that the two loci differentiated relatively recently (100–250 million years ago) [59, 60].

α_1-antitrypsin (AAT) deficiency

Alpha-1 antitrypsin (AAT) deficiency is a hereditary disorder first reported in the early 1960s when emphysema was described in patients with low plasma levels of AAT protein [4, 10, 13].The condition is related with substantially increased risk for the development of pulmonary emphysema by the third or fourth decades of life and is also associated with risks for development of hepatic disease [34], cutaneous panniculitis [25], bronchiectasis [37], vasculitis [40], Wegener's granulomatosis [7], and lung cancer [68]. AAT deficiency is characterized by misfolding of the AAT protein and belongs to a class of genetic diseases termed conformational disorders [18, 27].

The SERPINA1 gene is high pleomorphic with over 100 alleles identified to date [44].The most common mutation causing AATD is the Z mutation, with the S mutation weakly linked with lung disease. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. ATS/ERS guidelines advocate screening all COPD, poorly-controlled asthma, and cryptogenic liver disease patients, as well as first degree relatives of known AATD patients [12].

Epidemiology of α_1 - antitrypsin deficiency

The low frequency of the Pi ZZ phenotype in the general normal population makes firm data collection with respect to prevalence of affected individuals difficult to recieve. The prevalence of AAT deficiency in newborns has been expected from large population studies, with a screening of all newborns in Sweden in 1972 to 1974 being most comprehensive [15, 22]. Of 200,000 children in that study, 127 had the PiZZ phenotype, yielding a prevalence rate of approximately 1 in 1,600 newborns. Studies from various regions of Europe have shown a large variation in frequency of the Z gene in different countries [35].The gene frequency is highest on the northwestern seaboard of the European continent and the mutation seems likely to have arisen in southern

Scandinavia. In the USA, therefore, Z gene frequencies are highest in individuals of northern of western European descent [40]. Over all, the prevalence in the general population in Western Europe is approximately 1 in 2,500. The distribution of the S gene is quite different: the gene frequency is highest in the Iberian Peninsula and the mutation is likely to have arisen in that region [9, 43]. The belief that AAT deficiency is a disorder which mostly affects white subjects has been, inpart, shaken by the analysis of the worldwide surveys performed by de Serres [22]. He provided evidence for a significant prevalence of both PI*Z and PI*S in populations from the Middle East and North Africa, Central and Southern Africa, and Central and South-East Asia, suggesting that AAT deficiency has prevailed over racial and ethnic boundaries [22]. α1-antitrypsin deficiency is widespread throughout the world, with significantly high prevalence in countries throughout the continent of Asia. It also is clear that α1-antitrypsin deficiency is not just a disease of Caucasians (or whites), but is prevalent in many different races throughout the world [23,56].

Clinical description

COPD and alpha 1 - antitrypsin deficiency. The lung manifestations of AAT deficiency include emphysema and chronic obstructive pulmonary disease (COPD) [19]. Variations in the gene coding for α1-antitrypsin (AAT), the most abundant protease inhibitor circulating in the blood, is the only established genetic risk factor for COPD [2, 31]. Emphysema is a chronic progressive lung disease characterised by abnormal permanent enlargement of airspaces as a result of destruction of alveolar walls[9,65]. Emphysema usually develops by the third to fourth decade in affected individuals who smoke cigarettes and may appear in the fifth or sixth decade in individuals who have never smoked [11, 47].

Children and adolescents with α-1 antitrypsin deficiency have not been shown to have significant lung function abnormalities [62]. Although a study of affected children with liver disease suggested a tendency to hyperinflation [64].

Registries of patients with AAT deficiency show that as many as 43% of patients have chronic sputum expectoration, as defined by Medical Research Council (MRC) criteria, even in non-smokers. Patients with chronic bronchitis tend to have more severe airflow obstruction and more extensive emphysema than those without, despite similarities in age and smoking history [46, 52, 53].

Deficient Z Variant

Individuals who are homozygous for the deficient Zvariant have circulating concentrations of AAT that areless than 15% of normal values and an accelerated rateof deterioration of lung function, even in the absence of smoking [5]. However, pulmonary emphysema develops at an earlier age in those individuals who are also smokers [20]. The low plasma and tissue concentrations of AAT are insufficient to protect the connective tissue of the lung from the action of neutrophil proteases. Although the PIZZ phenotype is undoubtedly a genetic risk factor for the development of COPD, there is considerable variation in the clinical expression of the deficiency [41]. This variability is not entirely attributable to the difference in exposure to tobacco smoke, since the rate of deterioration of lung function in ZZ individuals who are nonsmokers is also highly variable [8]. The clinical expression of AAT deficiency is also modified by polymorphisms in glutathione S-transferase P1, a subfamily of glutathione S-transferase that is widely expressed in all types of epithelial cells, including those of the lung, [16, 66] and that participates in the detoxification of electrophilic substances and products of oxidative stress caused by tobacco smoke [54].

Methods for the diagnosis of α_1-at deficiency

Procedures for testing for α_1-AT deficiency have been available since the 1960s, and new techniques have been introduced during the intervening years. These advances in methodology should facilitate the widespread application of more rapid, convenient and cost-effective tests for α_1-AT deficiency and thus lead to an increase in the numbers of individuals diagnosed with the disorder [12, 46].

The primary diagnostic test for AAT deficiency is an immunoassay that measures AAT concentration in plasma or serum [29]. Typically, AAT-deficient patients homozygous for the Z allele have plasma or serum concentrations 85% below normal; whereas, patients who are

heterozygous for both the Z and S alleles can have intermediate AAT concentrations (~60% below normal) [49].

Methods:

Alpha-1-Antitrypsin PhenotypR™ - Isoelectric Focusing (IEF)

Alpha-1-Antitrypsin (Serum) – Nephelometry (NEPH)

Alpha-1-Antitrypsin GenotypR™ - INVADER®-based detection of Pi Z and S alleles in genomic DNA [30]

Individuals with MZ and SS phenotypes have AAT concentrations that are 40% below normal [38]. The MZ and SS phenotypes are indicative of intermediate AAT deficiency and an increased risk of developing AAT deficiency-associated diseases [33]. The ZZ phenotype is associated with a severe AAT deficiency1 and predisposes children to liver disease and emphysema [31].

Although over 70 European alleles in the Pi gene are reported, most are private or rare. Approximately 95% of AAT-deficient patients are either homozygous for the Z allele or are heterozygous for both the Z and S alleles.2,9 This assay detects both of these common alleles, and can identify carriers and individuals at risk for AAT deficiency that is independent of AAT concentrations [21].

Clinical Utility: Diagnosis of AAT deficiency in the symptomatic patient and concomitant identification of familial mutation; The mutation in the Z allele accounts for 95% of AAT-deficient patients; The World Health Organization (WHO) recommends screening for AAT deficiency at least once in all Chronic Obstructive Pulmonary Disease (COPD) patients and in adults and children with asthma [50].

Genetic counseling and prenatal testing

When patients are identified as a new case of homozygous type Z alpha-1-antitrypsin deficiency, the issue of heritability for their children is frequently raised. It is less inconvenient for the children when first the other parent is investigated by isoelectric focusing or genotyping for alpha-1-antitrypsin. Since about 95% of individuals carry the MM phenotype, all children from parents with ZZ and MM type will carry the MZ type alpha-1-antitrypsin. If the parent is not MM, but is carrying a deficient allele next to the M allele (*i.e*. MZ), there is a 50% chance of ZZ genotype for every newborn from these parents and this can be confirmed in the child by isoelectic focusing of serum. Prenatal testing is not a routine procedure due to the low penetration of liver disease shortly after birth [61].

Treatment

At present, treatment options for alpha-1-antitrypsin deficiency are very limited. There are no randomized, placebo-controlled studies that provide proof of an effective cure [35]. Specific therapy for AATD-related lung disease, called augmentation therapy, is the periodic intravenous infusion of pooled human serum alpha-1antitrypsin (AAT). Concordant observational studies show that AAT augmentation therapy can slow the rate of FEV_1 decline among individuals with AATD-related emphysema [3, 17]. For treatment of lung disease, the ATS/ERS Statement recommends intravenous alpha-1-antitrypsin augmentation therapy for Pi ZZ individuals with FEV_1 between 35 and 65% of predicted [51]. In addition, the World Health Organization (WHO) recommends annual flu vaccination and a pneumococcal vaccine every 5 years [66]. Like in emphysema patients without alpha-1-antitrypsin deficiency, relief of breathlessness may be obtained with long-acting bronchodilators and inhaled corticosteroids [63].

Natural history and prognosis

Alpha-1-antitrypsin deficiency with its many genotypes and its manifestation in various organs is rarely observed in daily clinical practice and is frequently not diagnosed or misdiagnosed. On average, the delay from the first signs of disease to the correct diagnosis is several years [55].Several studies have shown that FEV1 is the most important predictor of survival of patients with emphysema due to alpha-1-antitrypsin deficiency (AATD). For individuals with an FEV1 below 20% of predicted, the 2 year mortality is 40% if not treated by a lung transplant [69]. Patients who have never smoked and who are detected by screening of affected family members turn out to have a normal life expectancy. Most of these AATD individuals (83%) are clinically healthy throughout adulthood and most will have liver enzyme abnormalities in early life [71]. All of these observations were performed more than 15 years ago and in the mean time computed tomography of the chest provided new analytical information on the quality of lung parenchyma, including the extent of emphysema. Dawkins *et*

al. reported that lung density values assessed by computed tomography have better associations with mortality in type Z alpha-1-antitrypsin deficiency than FEV1 [24].

Conclusion

Alpha-1-antitrypsin deficiency (AATD) is an underdiagnosed condition in patients chronic obstructive pulmonary disease (COPD). Preventive measures, such as smoking cessation, avoiding contact with pollutants, vaccine prevention of infections are measures that reduce the rate of progression of the disease. It is advisable to pre-clinical diagnostic of alpha1-antitrypsin deficiency that could determine the choice of occupation, place of residence, the lifestyle of an individual.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors equally contributed to this review article. They read and approved the final version of the manuscript.

References:

1. AADRSG; Survival and FEV1 decline in individuals with severe deficiency of alpha-1 antitrypsin (Alpha-1 Antitrypsin Deficiency Registry Study Group). Am J Respir Crit Care Med. 1998, 158, pp.49–59.

2. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease and asthma. Am Rev Respir Dis. 1986,136, pp.225–244.

3. [ATSERS] American Thoracic Society, European Respiratory Society: American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003, 168, pp.818-900.

4. *Bao J. J., Sifers R. N. et al.* Molecular evolution of serpins: homologous structure of the human α_1-antichymotrypsin and $_1$-antitrypsin genes. Biochemistry. 1987, 26, pp. 7755–9.

5. *Barker A. F., D'Silva R. G., Buist A. S.* Lung function and alpha 1-AT deficiency. In: Crystal RG, ed. Alpha 1-antitrypsin deficiency: biology, pathogenesis, clinical manifestations, therapy. New York: Marcel Dekker, 1996, pp.245–57.

6. *Barnes P. J.* Chronic obstructive pulmonary disease. // N. engl. J.Med.2000, 343, pp.269-280

7. *Barnett V. T., Sekosan M., Khurshid A.* Wegener's granulomatosis and alpha1-antitrypsin-deficiency emphysema: proteinase-related diseases. Chest. 1999, 116, pp. 253–255.

8. *Bascom R.* Differential susceptibility to tobacco smoke: possible mechanism. Pharmacogenetics. 1991, 1, pp. 102-6.

9. *Beckman L., Sikstrom C., Mikelsaar A., Krumina A., Kucinskas V., Beckman G.* Alpha 1 - antitrypsin (PI) alleles as markers of Westeuropean influence in the Baltic Sea region. Hum Hered. 1999, 49(1), pp. 52-5.

10. *Brantly M., Nukiwa T., Crystal R. G.* Molecular basis of alpha-1-antitrypsin deficiency. Am J Med. 1988, 84,pp.13–31

11. *Brantly M. L., Paul L. D., Miller B. H., Falk R. T., Wu M.* Clinical features and history of the destructive lung disease associated with alpha1 antitrypsin deficiency of adults with pulmonary symptoms. AmRevRespirDis. 1988 b,138, pp. 327-36.

12. *Brantly M. L., Wittes J. T., Vogelmeier C. F., Hubbard R. C., Fells G. A., and Crystal R. G.* Use of a highly purified alpha 1-antitrypsin standard to establish ranges for the common normal and deficient alpha 1-antitrypsin phenotypes. Chest. 1991, 100(3), pp. 703-8.

13. *Campbell E. J.* Alpha 1 - antitrypsin deficiency: incidence and detection program. Respir Med. 2000, 94, pp. 18–21.

14. *Carrell R. W., Lomas D. A.* Alpha1-antitrypsin deficiency – a model for conformational diseases. N Engl J Med. 2002, 346, pp. 45-53.

15. *Carroll T., O'Connor C., O'Brien G., Molloy K., Ferrarotti I., Luisetti M., O'Neill S, Mc Elvaney G.* Rare alpha-1 antitrypsin mutations in the Irish population. Eur Respir J. 2011, 38, Suppl 55, pp. 313.

16. *Cichy J., Potempa J., Travis J,* Biosynthesis of α1-proteinase inhibitor by human lung-derived epithelial cells. J Biol Chem. 1997, 272, pp. 8250–5.

17. *Chapman K. R., Stockley R. A., Dawkins C., Wilkes M. M., and Navickis R. J.* Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. COPD. 2009, 6(3), pp. 177-84.

18. *Crystal R. G.* Alpha 1-antitrypsin deficiency, emphysema, and liver disease. Genetic basis and strategies for therapy. J Clin Invest 1990, 85, pp. 1343–1352.

19. *Dawkins P. A., Dowson L. J., Guest P. J., Stockley R. A.* Predictors of mortality in alpha-1-antitrypsin deficiency. Thorax. 2003, 58, pp. 1020-1026

20. *De Meo D. L., Silverman E. K.* Alpha 1-antitrypsin deficiency. 2: genetic aspects of alpha 1-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. Thorax.2004, 59, pp. 259–264.

21. *De Serres F. J.* Alpha-1 antitrypsin deficiency is not a rare disease but a disease that is rarely diagnosed. Environ Health Perspect. 2003, 111, pp. 1851-4.

22. *De Serres F. J.* Worldwide racial and ethnic distribution of alpha-1antitrypsin deficiency. Chest. 2002, 122, pp. 1818-29.

23. *De Serres F. J., Blanco I., Fernández-Bustillo E.* Estimated numbers and prevalence of PI*S and PI*Z deficiency alleles of α_1-antitrypsin deficiency in Asia. Eur Respir J. 2006, 28, pp. 1091-1099

24. *Dowson L. J., Guest P. J., Stockley R. A.* The relationship of chronic sputum expectoration to physiologic, radiologic, and health status characteristics in alpha(1)-antitrypsin deficiency (Pi Z). Chest. 2002, 122, pp. 1247–55.

25. *Edmonds B. K., Hodge J. A., Rietschel R. L.* Alpha 1-antitrypsin deficiency-associated panniculitis: case report and review of the literature. Pediatr Dermatol. 1991, 8, pp. 296–299.

26. *Elliott P. R., Lomas D. A., Carrell R. W. et al.* Inhibitory conformation of the reactive loop of α_1-antitrypsin. Nat Struct Biol1996, 3, pp. 676–81.

27. *Elliott P. R., Abrahams J. P., Lomas D. A.* Wild type α_1-antitrypsin is in the canonical inhibitory conformation. J Mol Biol. 1998, 275, pp. 419–25.

28. *Elliott P. R., Pei X. Y., Dafforn T. R et al.* Topography of a 2.0 Å structure of α_1-antitrypsin reveals targets for rational drug design to prevent conformational disease. Protein Sci. 2000, 9, pp. 1274–81.

29. *Ferrarotti I., Scavini R., Campo I., Ottaviani S., Zorzetto M., Gorrini M., Luisetti M.* Laboratory diagnosis of alpha1-antitrypsin deficiency. Translational reseach. 2007,150, pp. 267-74.

30. *Ferrarotti I., Zorzetto M., Scabini R. P., Mazzola, Campo I, Luisetti M.* A novel method for rapid genotypic identification of alpha 1-antitrypsin variants. Diagn Mol Pathol. 2004, 13 (3), pp. 160-3.

31. *Fregonese L., Stolk J.* Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. Orphanet Journal of Rare Diseases. 2008, 3, pp. 16-18.

32. *Greene C. M., Miller S. D., Carroll T., McLean C., O'Mahony M., Lawless M. W, O'Neill S. J., Taggart C. C., Mc Elvaney N. G.* Alpha-1 antitrypsin deficiency: a conformational disease associated with lung and liver manifestations. J Inherit Metab Dis. 2008, 31 pp. 21–34.

33. Harvard School of Public Health. Costly Non communicable Diseases on Rise in Developing World. *http://www.hsph.harvard.edu/news/features/cover-age-in-the-media/global-health-noncommunicable-diseases-bloom/index.html.* Date last accessed: July 8, 2011.

34. *Hird M. F., Greenough A., Mieli-Vergani G. et al.* Hyperinflation in children with liver disease due to alpha-1-antitrypsin deficiency. Pediatr Pulmonol. 2000, 11, pp. 212–216.

35. *Hutchison D. C.* Alpha1 antitrypsin deficiency in Europe; geographical distribution of Pi types S and Z. Respir Med.1998, 92, pp. 367-377.

36. *Kim S. J., Woo J. R., Seo E. J. et al.* A 2.1 Å resolution structure of an uncleaved α_1-antitrypsin shows variability of the reactive centre and other loops. J Mol Biol. 2001, 306, pp. 109–19.

37. *King M. A., Stone J. A., Diaz P. T., Mueller C. F., Becker W. J., Gadek J. E.* Alpha 1-antitrypsin deficiency: evaluation of bronchiectasis with CT. Radiology. 1996, 199, pp. 137–141.

38. *Kozlova I.* New in the diagnosis and treatment of COPD. Kazakhstan Medical Journal. 2012; 6:13-15

39. *Lomas D. A., Mahadeva R.* Alpha1-antitrypsin polymerization and the serpinopathies: pathobiology and prospects for therapy. J Klin Invest. 2002, 110, pp. 1585-90.

40. *Luisetti M.*, *Seersholm N.* α_1-Antitrypsin deficiency. Epidemiology of α_1- antitrypsin deficiency. Thorax. 2004, 59, pp. 164-169

41. *Mc Closkey S. C., Patel B. D., Hinchliffe S. J., et al.* Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. Am J Respir Crit Care Med. 2001, 164, pp. 1419–24.

42. Memorandum from a WHO meeting α1-Antitrypsin deficiency. Bull World Health Organ 1997,75, pp. 397-415.

43. *Miravitlles M., Herr C., Ferrarotti I., Jardi R., Rodriguez-Frias F., Luisetti M., Bals R.* Laboratory testing of individuals with severe α_1-antitrypsin deficiency in three European centres. Eur Respir J.2010, 35, pp. 960-968.

44. *Mornex J. F., Chytil-Weir A., Martinet Y. et al.* Expression of the alpha-1-antitrypsin gene in mononuclear phagocytes of normal and alpha-1-antitrypsin-deficient individuals. J Clin Invest. 1986, 77, pp. 1952–61.

45. *Perlmutter D. H., Daniels J. D., Auerbach H. S., et al.* The α_1-antitrypsin gene is expressed in a human intestinal epithelial cell line. J Biol Chem. 1989, 264, pp. 9485–90.

46. *Piitulainen E., Eriksson S.* Decline in FEV1 related to smoking status in individuals with severe alpha1-antitrypsin deficiency (PiZZ). Eur Respir J. 1999;13(2):247-51.

47. *Potempa J., Korzus E., Travis J.* The serpin superfamily of proteinase inhibitors: structure, function, and regulation. J Biol Chem. 1994, 269, pp. 15957–60.

48. *Rabe K. F., Hurd S., Anzueto A. et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007, 176, pp. 532–55.

49. *Rao N. V., Wehner N. G., Marshall B. C. et al.* Characterization of proteinase-3 (PR-3), a neutrophil serine proteinase. Structure and functional properties. J Biol Chem.1991, 266, pp. 9540–8.

50. *Ryu S. E., Choi H. J., Kwon K. S. et al.* The native strains in the hydrophobic core and flexible reactive loop of a serine protease inhibitor: crystal structure of an uncleaved α_1-antitrypsin at 2.7 Å. Structure. 1996, 4, pp. 1181–92.

51. *Seersholm N., Wencker M., Banik N., Viskum K., Dirksen A., Kok-Jensen A., Konietzko N.* Does alpha-1 antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha-1 antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaftzur Therapie von Lungenerkrankungen (WATL) Alpha-1 AT study group. EurRespir J. 1997, 10, pp. 260–3.

52. *Seersholm N., Kok-Jensen A., Dirksen A.* Survival of patients with severe alpha 1-antitrypsin deficiency with special reference to non-index cases. Thorax. 1994, 49, pp. 695-8.

53. *Seersholm N., Dirksen A., Kok-Jensen A.* Airways obstruction and two year survival in patients with severe alpha 1-antitrypsin deficiency. Eur Respir J. 1994, 7, pp. 1985-1987.

54. *Seersholm N., Kok-Jensen A.* Clinical features and prognosis of life-time non-smokers with severe alpa-1-antitrypsin deficiency. Thorax. 1998, 53, pp. 265-268.

55. *Silverman E. K., Pierce J. A., Province M. A., Rao D. C., Campbell E. J.* Variability of pulmonary function in alpha-1-antitrypsin deficiency: clinical correlates. Ann Intern Med. 1989, 111, pp. 982-91.

56. *Silverman E. K., Chapman H. A., Drazen J. M. et al.* Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998, 157, pp. 1770–8.

57. *Silverman E. K., Sandhaus R. A.* Clinical practice. Alpha1-antitrypsin deficiency. N Engl J Med. 2009, 360, pp. 2749–57.

58. *Sobradillo V., Miravitlles M., Gabriel R., Jiménez-Ruiz C., Villasante C., Masa J. F., Viejo J. L., et al*. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000, 118, pp. 981-9.

59. *Stolk J, Seersholm N, Kalsheker N.* Alpha1-antitrypsin deficiency: current perspective on research, diagnosis, and management. Int J Chron Obstruct Pulmon Dis. 2006, 1, pp. 151–60.

60. *Stoller J. K., Aboussouan L. S.* α_1-antitrypsin deficiency. Lancet. 2005, 365, pp. 2225-36.

61. *Stoller J. K., Smith P., Yang P., Spray J.* Physical and social impact of alpha - 1-antitrypsin deficiency: results of a mail survey of the readership of a national newsletter. Cleve Clin J Med. 1994, 61, pp. 461-466.

62. *Sveger T., Piitulainen E., Arborelius M. J.* Lung function in adolescents with alpha 1-

antitrypsin deficiency. Acta Paediatr. 1994, 83, pp. 1170–1173.

63. *Tonelli A. R., Rouhani F., Li N., Schreck P., Brantly M. L.* Alpha-1 antitrypsin augmentation therapy in deficient individuals enrolled in the Alpha-1 Foundation DNA and Tissue Bank. Int J Chron Obstruct Pulmon Dis. 2009, 4, pp. 443–52.

64. *Wall M., Moe E., Eisenberg J., et al.,* Long-term follow-up of a cohort of children with alpha-1-antitrypsin deficiency. J Pediatr. 1990, 116, pp. 248–251.

65. *Wencker M., Banik N., Buhl R., Seidel R., Konietzko N.* Long-term treatment of alpha-1 antitrypsin deficiency-related pulmonary emphysema with human alpha 1 - antitrypsin. Wissenschaftliche Arbeits gemein schaft zur Therapie von Lungener krankungen (WATL) – alpha -1 AT - study group. Eur Respir J. 1998, 11, pp. 428–33.

66. World Health Organization. Global Surveillance, Prevention and Control of Chronic Respiratory Diseases: a Comprehensive Approach. Geneva, WHO Press, 2007. P.317.

67. World Economic Forum. Global Risks 2010: a Global Risk Network Report. Geneva, World Economic Forum, 2010. p. 377.

68. *Yang P., Bamlet W. R., Sun Z., Ebbert J. O., Aubry M. C., Krowka M. J., Taylor W. R., Marks R. S., Deschamps C., Swensen S. J. et al.* Alpha 1 - antitrypsin and neutrophil elastase imbalance and lung cancer risk. Chest. 2005, 128, pp. 445–452.

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