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REVIEW ARTICLE

Chronic obstructive pulmonary disease in farmers and agricultural workers – an overview

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common inflammatory disease of the airways characterized by airflow obstruction that is not fully reversible. It is most often caused by smoking, but other factors including exposure to biological agents can play a significant role in its development. It is one of the leading causes of morbidity and mortality among the adult population worldwide. In Poland, symptoms of chronic impairment of airflow are present in 8.5% of males and 4.9% of females. Livestock farmers have an increased risk of chronic bronchitis, COPD, and reduced forced expiratory volume (FEV1). COPD in farmers working inside confinement buildings is related to organic dust exposure and may become severe. The management of COPD is aimed at improving the patient's quality of life and functional status. Currently, apart from lung transplantation, there is no treatment that would significantly improve lung function and decrease mortality. This led us to the conclusion that we should study the problem further, and cautiously monitor patients to help efforts aimed at the prevention of respiratory diseases among farmers and agricultural workers.

Key words

COPD, epidemiology, farmers, agriculture, organic dust, exposure

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common inflammatory disease of the airways characterized by chronic obstruction of airflow that is not fully reversible. It has been linked with multiple co-morbid conditions including cardiovascular diseases, diabetes mellitus, renal insufficiency, osteoporosis, psychiatric disorders and cognitive dysfunction [1-9]. According to the definition of the American Thoracic Society (ATS) it is a 'disease state characterized by chronic airflow limitation due to chronic bronchitis and emphysema'. Chronic bronchitis has been defined as the presence of chronic productive cough for at least 3 consecutive months in 2 consecutive years. According to Polish Society of Lung Diseases: 'COPD is characterized by poorly reversible, ongoing impairment of airflow through airways, which develops in people usually presenting with chronic bronchitis and/or emphysema. In spirometry, the FEV1/FVC ratio is less than 70%. Airflow impairment is related to inflammation, mainly in the distal airways, which cause obstruction and lead to pathological remodeling of the lungs. Those changes are the effect of lungs reaction to cigarette smoke, dusts and gases'[10].

Epidemiology: COPD is one of the leading causes of morbidity and mortality amongst the adult population worldwide [11]. In the developed regions of the world it is the fourth most common cause of death after cardiovascular diseases, malignancies, and deaths related to accidents. Furthermore, the share of COPD-related deaths in the total number of deaths is increasing, with the prognosis that by 2020 COPD will be third most common cause of death in the world. The Burden of Obstructive Lung Disease (BOLD) study found a global prevalence of 10.1%. Pooled prevalence among men was found to be 11.8%, and woman 8.5%, but the numbers vary in different regions of the world. The highest prevalence was noted in Africa and the lowest in Germany. COPD-related mortality in Europe varies from 10/100,000 in Greece, France, Spain and the UK, up to around 40/100,000 in Germany, Belgium, Denmark, Sweden, Norway, Russia, Romania, and Hungary. In Poland, symptoms of chronic impairment of airflow are present in 8.5% of males and 4.9% of females. Among the known risk factors of COPD, smoking has the strongest association with a relative risk of 4.3 in males and 2.3 in females. A recent study performed in Warsaw by Pływaczewski *et al.* [14] showed that in the age group between 41-72, COPD was diagnosed in 10.7% of subjects (10.9% of males and 10.3% of females). Among smokers, respondents over the age of 40 who took part in voluntary respiratory testing, 23% had significant obstruction. If the above-mentioned data is applied to the general population of Poland, it may be expected that there are circa 2 million patients in the country, which makes COPD the third most common chronic disease. In 2001, the rate of hospital admissions related to COPD were 41.9/10,000 for males and 24.2/10,000 for females. In 1999-2000, COPD was the cause of death in 2.6% of males and 1.3% of females, with a mortality rate of 19.6/100,000 (28,0/100,000 for males and 11.6/100,000 for females), thus making it the fourth most common cause of death. Among the known risk factors of COPD, smoking has strongest association with relative risk of 4.3 in male and 2.3 in female.

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Pollution of the air in the home environment is less significant, but nevertheless very important. In developing countries, exposure to indoor air pollution, caused by the use of biomass as fuel for cooking and heating, contributes to the overall COPD morbidity. In such communities, burning biomass is responsible for more cases of COPD than smoking or outdoor pollution. A high prevalence of COPD among non-smoking females in parts of the Middle East, Africa, Asia and America are considered to be caused by the widespread use of biomass fuels for cooking [15,16]. Exposure to polluted air in the workplace is also very important, especially among specific groups, including farmers and agricultural workers. Eduard *et al.* [17] found that the factors most strongly associated with chronic bronchitis in this group were exposure to ammonia, hydrogen sulfide, and inorganic dust.

Research into COPD in agricultural workers dates from 1989, when Dalphin *et al.* studied the prevalence of bronchitis and respiratory function in French dairy farmers, and concluded that they are at risk of chronic bronchitis and bronchial obstruction [18]. Greskevitch *et al.* [19] examined the 1988-1998 National Centre for Health Statistics 'Multiple Cause of Death Data' and the 1988-1994 Third National Health and Nutrition Examination Survey data (NHANES III) to evaluate respiratory-related mortality and morbidity among agricultural workers. They determined proportionate mortality ratios (PMRs) for respiratory conditions among 6 groups: crop farm workers, livestock farm workers, farm managers, landscape and horticultural workers, forestry and fishery workers. They also determined prevalence ratios (PRs) for 12 respiratory conditions among 3 agricultural groups: farm workers, farm managers, and other agricultural workers. Data analysis revealed the fact that crop farm workers and livestock farm workers had significantly elevated mortality related to respiratory conditions. Mortality for hypersensitivity pneumonitis was between 10 - 50 times higher than expected. Landscape and horticultural workers had significantly elevated mortality for lung and mediastinum abscesses and chronic airways obstruction. Forestry workers had a higher than expected mortality for TB, pneumonia, and chronic airways obstruction. The prevalence of asthma was high among agricultural workers who had previously been smokers. Finally, the study showed that farmers had a PR of 173 for obstructive respiratory abnormalities.

Monsó *et al.* [20] studied non-smoking animal farmers working inside confined buildings and found COPD in 18 of 105 farmers (17.1%). In 8 cases (7.6%), the disease was moderate and in 3 cases (2.9%) severe. They also found a dose-related relationship between COPD, dust, and endotoxin exposure, with the highest prevalence of COPD among subjects with high exposure to both dust and endotoxin.

Eduard *et al.* [17] compared the likelihood of chronic bronchitis and COPD among crop farmers and livestock farmers. Livestock farmers were more likely to suffer from both those conditions, with an odds ratio for COPD of 1.9 (95% confidence interval [CI]: 1.4 to 2.6), and for COPD – 1.4 (95% CI: 1.1 to 1.7). They also assessed the subjects' lung function and the effect of exposure to biological agents. The forced expiratory volume in one second (FEV1) was significantly reduced (-41 mL; 95% CI: -75 to -7), while the forced vital capacity (FVC) was not. Exposure to most of the biological agents predicted respiratory morbidity, but the effects of specific substances could not be assessed. Farmers with atopy had a significantly lower FEV1 (OR= -87 mL; 95% CI: -170 to -7). There was no significant relationship beetwen atopy, chronic bronchitis, COPD and FVC, but the effects of exposures on COPD were substantially greater in farmers with atopy.

Symptoms and diagnosis.

COPD can manifest itself in a number of ways, from fatigue on exertion to multiple respiratory symptoms (dyspnea, cough, increase in sputum production). The chronic cough initially occurs in the morning, but later appears throughout the day. Sputum is normally mucoid, but becomes purulent during infection-related exacerbations. Other symptoms of acute exacerbation include increased cough, wheezing, and dyspnea, often accompanied by fever. In the early stages of the disease physical examination can be normal. Later, with the increasing airway obstruction, it may reveal decreased breath sounds, wheezing, crackles at the lung bases, and hyperinflation of the chest [21]. Patients with severe COPD may present with additional symptoms, such as compulsory body position (sitting leaning forward), use of the accessory respiratory muscles, exhalation through pursed lips, retraction of the lower interspaces during inspiration (Hoover's sign), and cyanosis.

COPD should be suspected in all patients presenting with the above-mentioned symptoms and a history of exposure to tobacco smoke or occupational chemicals and dusts [19], including biological agents. COPD is diagnosed with pulmonary function tests (PFTs) that allow determination of the extent of airflow obstruction and monitoring of disease progression.

Pathogenesis and natural history.

The most common cause of COPD in the general population is exposure to tobacco smoke. Infections (both bacterial and viral) are the main cause of exacerbations in the course of the disease, and are also considered to be a factor in its pathogenesis [22]. In specific groups, other factors also play a significant role, e.g. in agricultural workers and farmers those factors include exposure to dusts and biological agents. There is a considerable variability in susceptibility to COPD that is still not fully understood. Until recently, the only confirmed inherited COPD risk factor was a deficiency of a1-antitrypsin, present in up to 2% of patients. In 2009, Pillai *et al.* in their genome-wide association study [23] evaluated the top 100 single nucleotide polymorphisms (SNPs) in the family based International COPD Genetics Network (ICGN). The SNPs showing replication were further analysed in subjects from the US National Emphysema Treatment Trial (NETT), controls from the Normative Aging Study (NAS), and in individuals from the Boston Early-Onset COPD population. Two SNPs at the two subunits of the a-nicotinic acetylcholine receptor (CHRNA3 and CHRNA5), that were earlier associated with lung cancer and tobacco dependence, were identified as showing unambiguous replication in the ICGN family-based analysis and in the NETT case-control analysis with combined p-values of 1.48610210 x 10(-10), (rs8034191) and 5.74610210 x 10(-10) (rs1051730). These polymorphisms were also significantly associated with lung function in both the ICGN and Boston Early-Onset COPD populations. Wilk *et al.* [24] were able to associate HHIP locus with lung function in the Framingham Heart Study, and Van Durme *et al.* [25] showed that variation near the HHIP gene was significantly associated with risk of COPD, depending on the smoking history of the subjects.

Obeidat et al. performed a meta-analysis of genome wide association study results for PFT's in individuals from the general population, but they were not able to prove the association between PFT's and polymorphisms of genes previously associated with lung function [26].

Inflammation is believed to be a major cause of lung damage and it is chronically present in the lower respiratory tract of patients with COPD. Sahlander *et al.* [27] studied immune response in farmers and smokers. They hypothesized that T-helper (Th) cell cytokine profile and acute response to pro-inflammatory stimuli that are considered to be markers of innate immunity differ between healthy, non-exposed subjects, smokers, and farmers chronically exposed to organic agents. The studied group comprised of 11 non-smoking pig farmers, 12 non-farming smokers, and 12 controls. Subjects underwent bronchial lipopolysaccharide (LPS) challenge and 3-hour exposure in a pig barn on separate days. Toll-like receptor 2 (TLR2), TLR4 and CD14 on monocytes and neutrophils and intracellular cytokine profile of Th cells were assessed before the exposure and 7 hours after. Tests were performed *in vivo* (peripheral blood cells) and *ex vivo* on purified neutrophils from farmers and controls after stimulation with dust from a pig barn and LPS. Th cells producing IL-13 and IL-4 and circulating neutrophils were increased in smokers and farmers. TLR2 expression on blood monocytes was decreased in farmers compared with controls and smokers. Altered TLR expression was only observed in controls after *in vivo* exposure, and the *ex vivo* stimulation resulted in weaker response in farmers compared to the control group. The altered response to pro-inflammatory stimuli in farmers and smokers was probably caused by adaptive mechanisms that develop during chronic exposure to organic agents. The resulting increase in Th2 cells and reduced TLR2 expression may be related to the increased prevalence of respiratory disorders among people from those groups.

Sundblad *et al.* [28] studied the effects of exposure to organic material on inflammatory response and airway reactivity. They attempted to prove that farmers and smokers show airway responses to inhaled organic and pro-inflammatory agents that are altered comparing to general population. Three groups (farmers, smokers and controls) were exposed to lipopolysaccharide (LPS) and 3-hours in a pig stable. Researchers assessed lung function, exhaled nitric oxide, and bronchial responsiveness. Nasal lavage fluid and induced sputum were collected for analysis and subjects' symptoms and body temperatures recorded before and after exposures. Bronchial responsiveness, exhaled nitric oxide, sputum IL-6, nasal lavage cell count and IL-8 after pig barn exposure were significantly increased in controls compared to farmers. Concentration of IL-6 in sputum after LPS challenge was also lower in the farmers. Smokers showed a response that was similar to that of the control group regarding measurements of exhaled nitric oxide, IL-8 in nasal lavage and IL-6 in sputum. On the other hand, bronchial reactivity and cell numbers present in nasal lavage was more similar to that of farmers. Sputum IL-8 increase after LPS challenge was more pronounced in smokers than in the other groups.

Milanowski *et al.* [29,30] studied the influence of organic dust on the chemotaxis of lung cells. Their *in vitro* tests proved that the microbial products were able to attract alveolar macrophages and neutrophils, and that the exposure of cultured alveolar macrophages stimulated chemotactic activity. They concluded that this mechanism may be responsible for the initiation and amplification of inflammatory reactions in the lung after inhalation of organic dust.

Golec *et al.* [31] studied the levels of cytokines, cathelicidin LL-37, granzymes, and TGF-beta1 in farmers with and without COPD. The studied group comprised 30 farmers with early stage of COPD, 36 healthy farmers and 16 healthy urban dwellers. Induced-sputum sampling and lung function testing were performed before and after work. Sputum samples from farmers with COPD showed significantly higher levels of LL-37 compared to healthy individuals. Sputum concentration of LL-37 and granzymes A and B in farmers was significantly higher than in urban dwellers. The results suggest that elevated levels of LL-37 and granzymes A and B may increase the risk of COPD and confirm their role in the response to organic dust exposure.

Factors affecting the natural course of COPD have a diverse background, and probably most of them are still undiscovered. The clinical outcome of COPD is most commonly linked with the reduction of FEV1, with other prognostic factors including smoking, low body-mass index (BMI ≤21), increased airway bacterial load, decreased exercise capacity, low peak oxygen consumption (VO2), elevated C-reactive protein (>3 mg/L), male gender and emphysema present in chest CT.

Four factors including weight (BMI), airway obstruction (FEV1), dyspnea (Medical Research Council dyspnea score), and exercise capacity (six-minute walking test) were used to develop the BODE index that allows for risk assessment in patients with COPD. Histamine-induced airway hyper-responsiveness was demonstrated to be a predictor of increased mortality [32]. Patients with COPD are often hospitalized due to disease exacerbations, which are most commonly related with respiratory tract infections. In-hospital mortality correlates with advanced age, prolonged hospital stay before ICU admission, severe respiratory, and severe non-respiratory organ dysfunction [33,34]. Acute respiratory failure due to exacerbation does not appear to decrease long-term survival. In a study by Martin et al., 2-year survival of patients with acute respiratory failure caused by COPD showed no difference compared to a control group with similar baseline pulmonary function tests (PFT's) [35].

Management of COPD

The management of COPD is currently universally based on recommendations provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [36]. It is aimed at improving patients' quality of life and functional status by preserving optimal lung function, reducing symptoms of the disease, and preventing acute exacerbations. There is no medical treatment that would significantly improve lung function or decrease mortality, but comprehensive disease management strategy is associated with lower hospitalization rate and decreased frequency of emergency department visits [37]. Oral and inhaled medications are used for patients with stable disease to reduce dyspnea and improve exercise tolerance. In stage I (mild obstruction), the treatment concentrates on reducing the risk factors and improving dyspnea by the use of the short-acting bronchodilators on an as-needed basis. In stage II (moderate obstruction), long-acting bronchodilators and cardiopulmonary rehabilitation are added. Stage III (severe obstruction), requires the introduction of inhaled glucocorticoids. Stage IV (very severe obstruction or moderate obstruction with evidence of chronic respiratory failure), often requires long-term oxygen therapy.

Studies have demonstrated survival benefit in patients using supplemental oxygen, but only if was used throughout most of the day. Patients with persistent hypercapnia can benefit from non-invasive ventilation. In the most severe cases, surgical options such as lung volume reduction surgery (LVRS) and lung transplantation are taken into consideration.

SUMMARY

Chronic obstructive pulmonary disease (COPD) is a common inflammatory disease of the airways characterized by airflow obstruction that is not fully reversible. It is most often caused by smoking, but other factors including exposure to biological agents can play a significant role in its development. Until recently, the only confirmed inherited COPD risk factor was a deficiency of a1-antitrypsin, but latest research suggest that SNPs at the two subunits of the a-nicotinic acetylcholine receptor (CHRNA3 and CHRNA5) and variation near the HHIP gene can be significantly associated with lung function and the risk of COPD.

Livestock farmers have an increased risk of chronic bronchitis, COPD, and reduced FEV1. COPD in farmers working inside confinement buildings is related to dust exposure and may become severe. Those findings suggest that problem must be studied further and patients cautiously monitored to assist with efforts aimed at the prevention of respiratory diseases among farmers and agricultural workers.

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