Asthma in the elderly

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Abstract: A population aged 65 and over has been increasing in the developed countries. The prevalence of asthma in elderly patients is estimated between 6.5 and 17%. Asthma is an important cause of morbidity and mortality in the elderly. Moreover, death due to asthma occurs mostly in elderly patients. Only a few studies have reported the characteristics of asthma in the elderly patients. Two distinct clinical presentations of asthma have been described in the elderly. There are differences both in the pathophysiology and the clinical manifestation of asthma between elderly patients with a long-standing disease and those with late-onset disease. Additionally, aging of the respiratory system influences the asthma presentation. Asthma has been presented for many years may lead to persistent obstructive ventilatory defect and can mimic chronic obstructive pulmonary disease. Irreversible obstruction is commonly observed in elderly patients with asthma. The differential diagnosis of asthma is difficult in older adults and asthma is underrecognized and undertreated in the older population. Undertreatment is common in elderly asthmatics which largely is related to diagnostic issues.

Key words: aging, airway obstruction, bronchial hyperresponsiveness, bronchial remodeling, late-onset astma

INTRODUCTION

In developed countries, a population of the elderly is growing. Respiratory system complaints common for this age group are major factors affecting mortality [1]. Despite problems with determination of its actual prevalence, bronchial asthma could be considered a common disease in the elderly, and according to epidemiological data, a proportion of people suffering from asthma in this population is estimated at 6.5–17% [2]. Deaths resulting from asthma occur mostly among the elderly patients. Death rate associated with bronchial asthma is clearly diversified depending on a patient's age: in a group of patients aged 55–59 it is 2.8 per 100,000 people, whereas in patients aged 60–64 it is 4.2 [3]. It is a well-known fact that this rate tends to decrease by 6% a year in younger age groups, whereas in patients aged 65–74 it decreases only by 2%, and in persons over 75 this decrease is not observed [4].

Therefore, the data on asthma in the elderly being frequently undiagnosed and inadequately treated [5,6] are alarming. Diagnostic and therapeutic problems seem to be a consequence of differences related to the disease clinical manifestations in the elderly patients.

It is known from epidemiological studies that bronchial asthma incidence rate reaches the highest values in childhood, and then it is maintained at a stable level in older age groups [7]. Therefore, discussing a phenomenon of bronchial asthma in the elderly, a division of patients into two groups shall be considered. The first group shall include patients with a long-standing asthma, whose symptoms occurred before the age of 65, and the second group shall include patients, in whom the symptoms occurred after the age of 65.

It is worth mentioning a historical study by Lee and Stretton [8] on patients with late-onset (after the age of 65), severe bronchial asthma. Attention should, however, be paid to the fact that the study involved a small, 15-person group, mostly smokers complaining of a long-standing productive cough. In the study by Quadrelli et al. [9], the elderly with diagnosed late-onset asthma had similar intensity of disease symptoms to the young patients. Patients with a long-standing disease, contrary to the late-onset asthma patients, had a shorter symptom-free period, increased number of hospitalizations and emergency medical interventions during a year, as well as lower values of ventilation parameters. Braman et al. [10] observed that among elderly asthma patients, subjects with a long-standing disease have considerably impaired lung function, which results in symptoms similar to the ones observed in a chronic obstructive pulmonary disease (COPD). Contrary to the aforementioned researchers, Burrows et al. [11] did not found relations between the disease duration and its severity. Those authors showed that the course of bronchial asthma in the elderly patients, despite considerable ventilation impairment, in long-term follow-up is not characterized by a rapid deterioration.

The observed discrepancies show that elderly patients diagnosed with bronchial asthma are a composite group. Additional difficulties occurring during attempts to characterize bronchial asthma in elderly patients result from the fact that the changes due to advanced age of studied persons overlap with the disease manifestations.

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Lung function

Along with ageing, gradual impairment of lung function is observed, expressed by a decrease in some parameters, e.g. forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and Tiffeneau index (FEV_1%/VC). However, in advanced age those changes are accelerated [12], and consequently the normal range, based on the extrapolation of results obtained in younger age groups, is overstated. According to Garcia-Rio et al. [13] studies on the European elderly population, the average value of FEV_1%/FVC index (called pseudo-Tiffeneau index of significance similar to Tiffeneau index), which for the 65-year-old subjects is 80% for females and 79% for males, is gradually decreasing to reach 70% for females and 73% for males in the group of 85-year-old people. At the same time, a low normal range in the analyzed age bracket is 68–71% for females and 64–70% for males. Therefore, accepting a Tiffeneau index of 70% of the predicted value, in order to distinguish between the healthy and the obstructive ventilation disorder patients, results in too common diagnoses of those disorders in the elderly.

In elderly asthma patients, a degree of lung function impairment depends on disease duration and severity of its clinical course, as well as on age. The factors including the time since diagnosis or the disease phenotype have an impact on a progressing decrease in FEV_1 values. An increased annual decline in FEV_1 values is observed in patients with newly diagnosed disease [14] and in the course of early-onset non-atopic asthma, phenotypically predominant in patients at advanced age [15].

Impairment of lung function ventilation parameters already at the time of bronchial asthma diagnosis in an elderly patient is a frequent phenomenon (Tab.) [16]. Its relation to delay in the diagnosis and commencement of treatment is probable – for an elderly patient, the delay may reach months or even years [16]. In a study by Bellia et al. [5] in over 27% elderly patients with bronchial asthma, no respiratory disease has been diagnosed.

Reversibility of airway obstruction and recognition

The bronchial reversibility test is a basic test enabling distinguishing between bronchial asthma and COPD. In the elderly, both with and without asthma diagnosis, impairment of β_2 adrenergic receptor function is observed [17]. The impact of age on activity of cholinergic receptor in healthy persons [18] has not been presented. On the other hand, in asthmatic patients, bronchodilation response upon administration of cholinolytic agent decreases with age, but this decrease in reactivity of M_1 and M_3 muscarinic receptor is less clear than in the case of β_2-mimetic agent administration [19]. Therefore, bronchial reversibility tests in the elderly should be carried out with the use of short acting β_2-mimetic and cholinolytic agents.

A positive obstruction reversibility test following the use of bronchodilator is an important guide that confirmsthe diagnosis of bronchial asthma, it is not, however, an absolute condition for the diagnosis. The elderly asthmatic patients may show improvement of lung function parameters in the spirometric test only upon administration of systemic corticosteroids. Asthmatic inflammation, as well as chronic administration of β_2-mimetic agents, results in a decrease in expression of β_2-adrenergic receptors and their affinity to the drug. The so-called permissive action of corticosteroids on β_2-mimetic response may be explained among others by their effect limiting those processes [20,21]. The elderly long-lasting asthma patients, in comparison with the elderly late-onset asthma patients, have lower FEV_1 and FEV_1%/FVC values both before and after the use of bronchodilator, thus showing features of fixed obstruction (Tab.) [10].

Airway remodeling

Long-standing bronchial asthma may generate development of fixed obstruction, related to damage to the bronchus wall by long-lasting asthmatic inflammation, which causes airway remodeling. The process involves numerous profibrinolytic mediators: first of all transforming growth factor β, as well as interleukin 11, interleukin 13, interleukin 17, or adenosine [22,23]. Remodeling is a complex process comprising among others thickening of the reticular layer of basement membrane, an increase in collagen deposition in intracellular matrix, epithelial fragmentation, hypertrophy and hyperplasia of airway smooth muscles, hyperplasia of mucous glands and vascular proliferation [24]. These lesions may appear quite early in the course of disease [25], leading in time to structural lesions in the lung parenchyma, manifesting itself in fixed airflow impairment in the respiratory tract due to narrowing of the bronchial lumen. Airway remodeling, appearing as a reaction to damaging factors, including inflammation, is not a phenomenon observed only in bronchial asthma. Inflammation and remodeling appear both in bronchial asthma and in COPD, differing, however, in the anatomical location, type of tissue structures undergoing remodeling and profile of cells involved in those pathological processes [26]. Moreover, impairment of the systemic immune response to infections observed in the elderly, translating into their more severe clinical course, may also result in development of chronic respiratory tract inflammation and its remodeling [27].

According to Cassino et al. [28], the disease duration was inversely correlated with the reached FEV_1 values. Following the use of bronchodilator, normal FEV_1 values were observed only in 18% of asthma patients with long disease duration, whereas in the elderly patients diagnosed with asthma with shorter disease duration, a normal value of this parameter was reached by >50% of patients. Similar results were obtained by Little [29], whose study demonstrated maximum FEV_1 value inversely proportional to the disease duration and the patient's age.

The presented data show that long-lasting asthma, leading to fixed airway obstruction, makes asthma clinically similar to COPD. Airway remodeling seems to be a factor responsible for

Table. Characteristics of asthma in the elderly

Features	Asthma in patients <65 years of age	Asthma in patients >65 years of age, previously diagnosed	Asthma diagnosed in patients >65 years of age
Asthmatic inflammation	Mastocytes, lymphocytes, $CD4^+$, eosinophils	Mastocytes, $CD4^+$, $CD8^+$ lymphocytes, eosinophils, neutophils	Mastocytes, $CD4^+$, $CD8^+$ lymphocytes, eosinophils
Pulmonary function	May be normal	Marked impairment	More profound annual decline in FEV_1
Obstruction reversibility	Frequently total	Frequently irreversible or poorly reversible	Greater FEV_1 and FEV_1%/FVC before and after use of bronchodilator
Bronchial hyperresponsiveness	Related to inflammation	Increasing with age – related to pulmonary function	Increasing with age – related to inflammation intensity

FEV_1 – forced expiratory volume in one second, FVC – forced vital capacity, FEV_1%/FVC – Tiffeneau index

development of this most typical of COPD pulmonary function impairment in patients diagnosed with asthma [30]. This process is most probably overlapped by structural changes related to lung ageing, defined as "senile lung" or "ageing lung" [31,32].Those changes first of all result from the reduced lung elastic recoil pressure, observed with ageing [33].

According to Bellia et al. [5], every fifth asthma patient is misdiagnosed with COPD. In the elderly, especially smokers, an attempt to distinguish between COPD and bronchial asthma, based on the FEV_1 values and the obstruction reversibility test, may prove difficult [11]. Seeking etiological factors of the impaired lung function in an elderly patient, due to lack of absolutely precise and separate definitions of bronchial asthma and COPD, may incline to diagnoses of an asthma/COPD overlap syndrome in some patients. The medical data review made by Soriano et al. [34] demonstrates that the probability of coexistence of obstructive lung diseases increases with the patient's age. Some bronchial asthma patients who were exposed to factors damaging the lung tissue may develop inflammatory process presenting some symptoms of both analyzed diseases.

However, the studies by Fabbri et al. [35] show that asthma patients who developed fixed ventilation disorders, in comparison to individuals diagnosed with COPD, have an increased number of eosinophils found in peripheral blood, induced sputum and BAL fluid, as well as an increased number of $CD4^+$ lymphocytes and an increased $CD4^+/CD8^+$ ratio.

On the other hand, in severe bronchial asthma with fixed obstructive disorders, an increased number of neutrophils similar to COPD is observed (Tab.) [36]. Neutrophils, by releasing proteolytic enzymes, participate in airway and lung parenchyma remodeling, thus in development of irreversible obstructive disorders [37]. Even more interestingly, Chanez et al. [38] observed reversible airflow obstruction upon the use of glycocorticosteroids (1.5 mg prednisolone for 15 days) in some COPD patients. Those patients manifested some features making their disease similar to bronchial asthma: slightly increased eosinophilia in bronchial lavage and thickening of reticular layer of basement membrane. These data demonstrate that the course of asthma, particularly in the elderly, may manifest fixed obstructive disorders [10], whereas in COPD a considerable reversibility of bronchial airflow obstruction may be observed.

Airway hyperresponsiveness

Airway hyperresponsiveness (AHR) increases with age. The prevalence of AHR in the adult population is 10–16% [39], whereas in the population of the elderly it is estimated at 29–43% [40,41]. An increase in AHR can also be observed with age in the elderly asthma patients [42].

There is a relation between markers of asthmatic inflammation in the respiratory tract and airway hyperresponsiveness. In bronchial asthma patients, a percentage of eosinophils in the respiratory tract is positively correlated with the degree of airway hyperresponsiveness [43]. Grönke et al. [44] observed it in individuals with shorter duration of the disease, whereas in patients with longer duration of the disease AHR depends on lung function parameters, which may be related to remodeling (Tab.).

There are interesting data showing a relationship between AHR and not only local airway inflammation, but also nonspecific systemic inflammation. Particular attention should be focused to C-reactive protein (CRP), one of the most important acute phase proteins, whose synthesis is regulated by interleukin 6, called "the gerontologist interleukin". Here, we can quote the studyby Kony et al. [45], which reflected associatios between increased CRP values and airway hyperresponsiveness in the general population, and a study by Tsunoda et al. [46], which reported a relation between airway hyperresponsiveness and interleukin 6 in pregnant women. Ólafsdottir et al. [47] indicated a relation between age and high sensitivity CRP (hsCRP) level. The same researchers observed that hsCRP level is statistically significantly higher in persons with diagnosed nonatopic asthma in comparison with patients with diagnosed atopic asthma and subjects without asthma.

Treatment

Principles of treatment of bronchial asthma in the elderly do not differ from those used in younger patients. Some spe-

cial therapeutic issues are related to advanced age. They include an increased probability of adverse effects of the applied agents, particularly in the case of other diseases coexistence in an elderly patient. Vital therapeutic difficulties are related to frequent polypragmasia in those patients, who also show incorrect drug use, particularly inhaled preparations. The cooperation between a physician and a patient with cognitive deficiency or a patient with impaired ability to move, needs to be focused on an appropriate application of inhaled agents of crucial significance in asthma therapy [48]. For an elderly individual, it is easier to use the inhalation chamber (spacer) along with metered dose inhalers, or dry powder inhalers [49]. However, dry powder inhalers require appropriate inspiratory flow, which excludes their administration to all patients [50]. In patients with significant cognitive deficiencies, nebulization may also be suggested [48].

The impact of age on impairment of the affinity of β_2 receptor to its agonists has been quite well documented by in vitro tests [17]. However, the data concerning bronchodilation response obtained upon the use of β_2-mimetics in the elderly are ambiguous. Some authors suggest that age influences its decrease, whereas others do not observe this relation [19,51]. However, among the relaxant agents, short-acting β_2-mimetics remain the basic agents of short-term treatment. Cholinolytic agents are their useful alternative, particularly in the case of partial relaxant effects and occurrence of adverse effects upon administration of β_2-mimetics. Inhaled corticosteroids are basic agents that control the course of the disease in the elderly prevent from adverse effects associated with systemc corticosteroid therapy [52]. Effectiveness of corticosteroid administration in patients with fixed obstruction may be assessed following the discussed 2-week trial treatment with systemic corticosteroids.

Despite crucial significance of corticosteroids in the bronchial asthma therapy, only every third elderly asthma patient receives inhaled corticosteroids [6]. A study by Sin et al. [53] seems alarming by showing that in as many as 40% of asthma patients over 65 years of age, who recently manifested asthma exacerbation requiring hospital admission, inhaled corticosteroids were not used. A greater probability of failure to administer inhaled corticosteroids was related to advanced age, the presence of other diseases and care provided for a patient by a primary care physician.

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