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Late onset asthma in the elderly and its relationship with atopy

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SUMMARY

Although asthma has always been considered as a disease of the early years, its presence is found both in old and young people. Asthma is often underestimated in the elderly because it can be confused with other diseases such as heart failure and, frequently, with COPD. In most cases asthmatic patients develop their disease before 45 years of age, but sometimes the first episode of asthma occurs after 60 years of age. This asthma phenotype is called Late Onset Asthma (LOA). LOA is often underestimated but, in recent years, some studies have shown that LOA is not entirely uncommon among the elderly; this clinical form is often caused by allergic sensitizations. The cause depends on the overall improvement of health in the most economically developed nations and also on the parallel increase in allergic diseases in these countries.

Generality of asthma in the elderly

Bronchial asthma is often a cause of respiratory symptoms, not only in adults or children, but also in elderly people. According to some studies the prevalence of asthma in adults varies between countries from 7% to 15%. Several studies have shown that the prevalence of asthma in the elderly is similar to that of other adult age groups, ie 4.5 to 8% (1-4). Although asthma has always been considered as a disease of the early years, its presence is found both in old and young people (5). There is not much evidence about the natural history of asthma in elderly patients. Asthma in the elderly is associated with an increased morbidity and a lower quality of life. However, elderly patients with asthma are underdiagnosed and underestimated (6).

Almost 20% of elderly asthmatic patients receives an improper diagnosis of COPD (7). The reasons for this underestimation may be due to diagnostic misclassification or under-reporting of symptoms (8). The difficulty of a diagnosis is due to a number of factors: the confounding role of smoking and also the physiological effects of ageing on the airways, which makes airway obstruction more resistant to bronchodilation, also by the remodeling (9). A further source of under-diagnosis is the heterogeneity of clinical cases (10). Allergic rhinitis and asthma in the elderly should be milder or almost absent (11). Furthermore, some studies suggest that sensitivity to indoor allergens are more prominently associated with the presence of asthma in an elderly population (12, 13). In this paper we deal mainly with late onset asthma in the elderly and its relationship with atopy.

Immunosenescence

Aging is associated with a decline in the immune system and the cells that performs a regulatory role in asthma, resulting in a decrease of functions of T lymphocytes, neutrophils and epithelial cells (14). The dysfunction of T lymphocytes may increase the susceptibility to infections, and enhanced neutrophil recruitment. A further consequence of this might be the excessive release of protease and oxygen free radicals, leading to airway inflammation and remodelling. Occurs, thus, a state of disregulated immune function that contribute to the increased susceptibility to infection. Infections, in turn, may contribute to amplification of the inflammatory response in the airways of asthmatic subjects with an increase in neutrophilic component. In elderly serum IgE levels and antigen specific IgE production both decline, in correlation with the reduction of allergic disease. However, in elderly asthmatic atopy can still play a significant role (15).

Factors affecting airways in the elderly

Asthma in the elderly often shows an accelerated functional decline and an increased risk of mortality (16). Age-related physiological changes occur in all elderly and can be grouped in three phenomena: 1) decrease in strength of respiratory muscles, 2) decrease in lung recoil, 3) increased stiffness of the chest wall (14).

Morphologic and physiologic changes have been observed in the aging human lung. These are represented by decreased mucociliary function, dilatation of the air spaces, loss of elastic recoil and of elastin fibers, decreased diffusion capacity, and evidence of low-grade inflammation of the respiratory tract (14). These abnormalities can add their effects to those produced by asthma. Most of the studies is in favour of positive association between age and airway hyper-responsiveness. Therefore, the assessment of airway hyper-responsiveness, in the aged, should be considered an additional tool in the diagnostic of asthma in elderly (17).

Some studies, indeed, suggest that severity of asthma and development of irreversible airflow obstruction depend on the duration of a disease. This is another reason that causes the onset of asthma in the elderly (10, 18).

The underdiagnosis may be due: poor perception of breathlessness, technical difficulties in making reliable pulmonary function measurements and the extra-pulmonary manifestations (impact on quality of life) (19).

Asthma in the elderly was associated with higher mortality rate, although this condition was not an independent risk factor. Causes of death and factors associated with death were somewhat different between people with and without asthma.

Asthma in the elderly, more so than in younger populations, may be due to iatrogenic causes. For instance, it can be associated with the use of medications including ASA, nonsteroidal anti-inflammatory drugs (NSAIDs) and adrenergic-blocking agents, including topical preparations. These drugs can cause asthma even at young age, but elderly use them more frequently, for the treatment of various co-morbidities.

Comorbidities

Additionally the clinical manifestations of asthma are complicated by comorbidities (20). A co-morbidity is usually defined as a disease coexisting with the disease of interest. Frequently used in research and practice, no definition of co-morbidity is uniformly accepted (21). In elderly patients with asthma co-morbidities are frequent and significantly influence their quality of life (10). The most frequently reported asthma co-morbidities include COPD, respiratory infections, rhinitis, sinusitis, gastro-oesophageal reflux disease, obstructive sleep apnoea, obesity, hormonal disorders and psychopathologies (22). These conditions, in different ways, depending on the clinical severity, may share a common pathophysiological mechanism with asthma or may influence asthma control, its phenotype and response to treatment. Finally, these co-morbidities may be more prevalent in asthmatic patients but without evident influence on this disease. In the elderly asthma is often associated with other diseases of old age, coexisting independently, such as coronary artery disease, hypertension, diabetes, bone diseases, Alzheimer disease. These diseases make management of asthma more difficult (23).

Moreover, asthma is often underestimated in the elderly because it can be confused with other diseases such as heart failure and, frequently, with COPD (24). In these diseases, some symptoms, such as dyspnoea, may resemble each other and confuse the diagnosis. Asthma and chronic obstructive pulmonary disease (COPD) are both characterized by the presence of airflow obstruction, reversible only in asthma. Both diseases are not rare in the elderly population; actually a distinction between these diseases is difficult and sometimes also impossible, especially when the patient is old (25). The high incidence of co-morbidities in the elderly makes

more difficult the diagnosis and management of this disease (26). Misdiagnosis can also be related to older age and to greater degree of disability. Asthma in patients with mild functional impairment may be underdiagnosed in spite of overt respiratory symptoms suggestive of asthma (7).

Late Onset Asthma (LOA)

Elderly asthmatics can be divided on clinical grounds into two arbitrary groups. A first group "ageing asthmatics" who have had asthma since childhood or adolescence (early-asthma). A second group, in which the onset of asthma occurs after 65 years of age (25, 27, 28). Regarding the first group we can say that the long-standing asthma obstruction leads to chronic persistent airflow and thereby mimics COPD (25).

In most cases asthmatic patients develop their disease before 45 years of age, but sometimes the first episode of asthma occurs after 60 years of age. This clinical form is called Late Onset Asthma (LOA). The definition of LOA is: "asthma with onset of symptoms in adult life in a patient with no pre-existing, persistent respiratory symptoms", but opinion of researchers differ on what that age should be (29). LOA is different from early onset asthma for functional and clinical features. LOA has also been associated with intrinsic asthma while early onset asthma is mainly associated with extrinsic asthma (30, 31).

The histopathology of LOA appears to be similar to that asthma in general, with persistent airway inflammation a characteristic feature. In LOA atopy is less common. IgE levels is lower among those aged over 55 years of age than younger patients. A correct diagnosis is achieved by good history and physical examination, the demonstration of reversible airways obstruction and a favorable response to treatment (32). LOA is recognized as a more severe asthma phenotype with a greater degree of airflow obstruction, more frequent exacerbations, and a greater rate of lung function decline (11).

In a study comparing asthmatics, aged over 70, with either early or late onset asthma, it was found that early onset of asthma was associated with significantly lower pre- and post-bronchodilator percent predicted FEV1 and FEV25-75 (25).

Early onset asthma, generally, remains relatively stable, but LOA is more severe and progressive and less reversible. Compared with early onset asthma, LOA has female preponderance, worse lung function, despite a shorter duration of illness and lower prevalence of atopy (30). Patients with

early-onset, severe asthma have significantly more skin tests positivity and more allergic symptoms than patients with LOA. The presence of eosinophils in either age at onset group is associated with the lowest lung function. LOA is associated with the highest number of lung eosinophils, but only early onset severe asthma is associated with a lymphocytic/mast cell inflammatory process. Moreover, patients with LOA without eosinophils have not sub-epithelial basement membrane thickening (31). This suggest a different pathologic process.

Differentiating features of Early Onset Asthma and Late Onset Asthma are shown in the Table 1.

Atopy and Asthma in elderly

Ageing is associated with modifications of the immune system and this could contribute to a reduction of the prevalence of allergic disease in the elderly. Atopy has rarely been considered in the clinical assessment of the geriatric respiratory patient. Many studies show that there is a lower prevalence of atopy in elderly (16). Anyway, it is well known among allergists, that allergic reactions in old people may show themselves in the same way, or even in a more severe way, than in younger people. For this reason, even if it seems that ageing favors the decline of sensitization to allergens, the prevalence of allergic sensitization in elderly people with respiratory symptoms remains significant, so it seems more useful to perform skin prick tests to evaluate the atopic condition (33).

Many years ago a study had demonstrated a correlation that level of serum IgE was a strong predictor of new-onset asthma in a population aged >60 years (34).

A few years later, another study found, in a population >65 years aged, a significant correlation between airway hyperresponsiveness and IgE and eosinophils count (35). In recent years, the role of atopy as regards diagnosis, therapy and prognosis of asthma in the elderly is revalued (17, 33).

A study showed an incidence rate of newly diagnosed asthma by 0.1% a year in those patients over 65 years of age (36). In a 1997 study Litonjua et al. (37) wanted to address the role of the allergic response to environmental aeroallergens in the development of asthma in a sample of older men. They demonstrated that there was a significant association between sensitization to cats and the presence of asthma in the group of older men. The authors concluded their paper by stating that in the research of causative factors and triggers of asthma in an elderly population,

Table 1 - Differentiating features of Late Onset Asthma and Early Onset Asthma

Characteristic	Late Onset Asthma	Early Onset Asthma
Age > 65	Common	No, only in early life
Family History	May be present	Frequently present
Skin tests positivities	Less common	common
Other allergic diseases	Less common	common
Risk factors	Irritant exposure, atopy	Atopy, airway hyper-responsiveness
Inflammation	Eosinophilic and neutrophilic	Eosinophilic
High IgE	Infrequent	Frequent
Infections	Common	Not common
Sex	F > M	M>F in child - M=F in adult
Smoking history	Less common	Not common
Episodic wheeze	Common	Common
Nocturnal dyspnea	Common	Common
Chest X ray	Often normal	Often normal
Response to beta2 agonists	Increase FEV1	Increase FEV1
FEV1 predicts	< 80%	> 80%
FEV1/FVC	< 70%	> 70%

sensitization to common aeroallergens should not be overlooked, and avoidance of allergens should be part of the management plan for those who are sensitized.

A few years ago, our group has done some research on asthma in the elderly (38) by comparing a group of asthmatic patients over 65 (average age 72), affected by LOA, with three other groups: the first group affected by early asthma, a second group affected by COPD, and a third group of healthy elderly. We also used an additional fourth control group of young asthmatics (average age 37). The groups were homogeneous as severity of asthma and respiratory function. The mean level of total IgE in LOA was almost the same in the young asthma group and higher than in the other groups and in the control group. The main allergen in LOA was *Dermatophagoides pteronyssinus* (75%) followed by pollens *Parietaria judaica* (36%) and grasses (14%). The prevalence of monosensitization was rather high (42%) compared to polysensitization (58%). The conclusion of our study was that LOA is not very rare even in the elderly and that, in most cases, allergy to the commonest aeroallergens is found.

Recently, other researchers have again analyzed similari-

ties between the elderly and young asthmatic patients and the not uncommon presence of LOA in the elderly (39), argues that while many asthmatics during their life may have a long period of remission and later a recidive of the disease, in some elderly people cases of LOA have been found. Although many differences occurring between asthma in the elderly and asthma in young people (medical comorbidity, fixed airway obstruction that resembles COPD, lack of perception of dyspnea), the patho-physiology and the clinical presentation of asthma in the elderly is similar to younger asthmatics.

Two other interesting articles on this topic have been produced by the University of Palermo group (40, 41). These authors made a review to assess the impact of the age on atopy. Though the literature suggests a low prevalence of atopy in the elderly -both healthy subjects and patients with allergic respiratory diseases- the authors underline the lack of wide longitudinal epidemiological studies.

Although the available data seem to favor the decline of allergen sensitization with age, the prevalence of allergic sensitization in the elderly with respiratory symptoms is substantial enough to warrant the assessment of atopic status. From

the clinical point of view, allergic reactions in older adults may have the same effects or, even worse than in younger people. For this reason, the evaluation of atopic status in the geriatric patient is also recommended. Thus, the role of atopy in regard to diagnosis, treatment (adoption of preventive measures, such as removing environmental allergens or immunotherapy), and prognosis (impact on morbidity and mortality) of chronic respiratory diseases in the elderly is addressed.

Elderly patients with asthma for a long time have more severe airway obstruction than patients that have recently acquired the disease. Older patients, especially those with long-standing disease, complain of fewer symptoms of asthma.

Within the various groups of patients, subjective symptoms of asthma were negatively correlated with the duration of asthma (42). With regard to the second group we can confirm that, if the diagnosis of asthma in old patients is easily overlooked, the late-onset asthma (LOA) is even more neglected.

Management of LOA

The management of LOA does not differ from that of asthma in general. There are, in this regard, four key points. First aim is the control of environmental exposures. Second, be sure that asthmatic subject is inhaling glucocorticoids properly. Older patients, often, have difficulties in using inhaler devices. Third, consider side effect of medications, such aspirin and beta-adrenergic inhibitors. Fourth, considering any associated lung disease. Aging has been associated with a reduced acute response to bronchodilators most likely ascribed to age-related decline in receptors functions or loss of receptors with aging (43). Moreover, long-acting beta-agonists have become controversial in patients with coronary artery disease. and overdose with SABAs or oral glucocorticoids can cause serious side effects. In this regard, aerosol anticholinergic agents are a practical substitute for beta-agonists (23).

Discussion

Asthma phenotypes

Asthma has long been considered as a heterogeneous grouping of syndrome, but much is still to understand about immunologic and pathologic differences among phenotypes. The traditional distinction in “allergic” and

“non-allergic” asthma it’s questionable by recent study that suggest small differences immunopathological between them (44). Also the traditional view of the low presence of atopy in elderly seems to bring into question by several evidence, which we described above.

LOA only intrinsic asthma?

In the past little attention was given to LOA, especially because there is no awareness of this form of asthma. However, it is usually believed, that this constitutes a form of intrinsic asthma, with no evidence of sensitization to common allergens. This is due to the fact that, generally, the diagnosis does not include allergic tests. Other reasons, about this topic, include the fact that the skin of the elderly is - because of its dryness - less reactive to skin tests, which in turn leads to the prejudice that it is useless to try to find a sensitization. A recent experience, however, has shown that in many of these subjects, both clinical symptoms and the production of specific IgE, skin prick test and RAST, are very similar to those of the younger population. The explanation for this clinical situation, which would seem to contradict what we know about the decline of immune system activity in the elderly, can find a basis on certain assumptions.

Latent atopy

The first hypothesis we put forth in our first work in 1998, shows that, as in the number of mono-sensitizations LOA is almost as high as in a group of individuals with latent atopy. This clinical entity may have resulted in a kind of suppression mechanism for IgE. This suppressive mechanism is still hypothetical and it depends on the loss of natural specific IgG4 antibodies to block, or to an imbalance of the Th1/Th2 system through an increase in Th2 cells.

Older Youth

A second hypothesis is based on the fact that in recent years there has been an increase of the average lifespan of the population and an overall improvement in general health. In the past 50 years the world has experienced enormous and unprecedented gains in the health of human population.

In recent decades, progress has been especially remarkable in developing countries where the average life expectancy has increased by more than 60 percent; actually in 1950

the life expectancy was 40 years, while at present it is 65 years (45). Thus, worldwide there has been an improvement in quality of life of older persons (46).

Besides this overall improvement, there was also an improvement, particularly with regard to the immunological assessment of the age over 65 years. Therefore, the overall improvement of health, has definitely shifted towards the older age of immunological decline. This situation makes possible for people over 65 to submit an immunological reactivity similar to that of younger age classes. Therefore, today, there is the possibility of new sensitizations in older age groups. This possibility was not considered, in the past, because the common thought was that older age groups were characterized by a decreased immunological reactivity. This essay gives an explanation of why some elderly subjects with features of atopy, may also sensitize later in life developing allergic asthma.

Conclusions

In conclusion, we believe the LOA is not entirely uncommon among the elderly, as it is usually believed and that, often, the most common allergy to aeroallergens is not searched routinely. Origins and the evolution of this clinical situation are attributable to the global improvement of the overall health, which brings also a parallel increase of allergic and respiratory diseases. However, we could also hypothesize that patients with late onset asthma have a different immunologic phenotype from those who had asthma early in life. We believe, therefore, that large longitudinal studies are needed, to better define the differences between these two phenotypes.

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