

Should atopy be assessed in elderly patients with respiratory symptoms suggestive of asthma?

Expert Rev. Resp. Med. 4(5), 585–591 (2010)

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Aging is associated with modifications of the immune system and this could contribute to a reduced prevalence of allergic disease in the elderly. Atopy has rarely been considered in the clinical assessment of the geriatric respiratory patient. This article is a review of the available literature assessing the impact of age on atopy in the asthmatic patient. In the majority of papers, we found a lower prevalence of atopy in the most advanced ages, both in healthy subjects and in individuals affected by allergic respiratory diseases. No large, longitudinal studies performed in the general population have been conducted to confirm this observation. Although available data seem to favor the decline of allergen sensitization with age, the prevalence of allergic sensitizations in the elderly population with respiratory symptoms is substantial enough to warrant evaluation of the atopic condition. For this reason, the evaluation of the atopic condition in the geriatric patient is recommended. The role of atopy as regards diagnosis, therapy and prognosis of asthma in the elderly is addressed.

KEYWORDS: aging • allergen • asthma • IgE • skin-prick test

Atopy is a term that refers to the predisposition to develop allergic diseases, namely allergic rhinitis, asthma, atopic dermatitis and food allergy. The definition of the atopic condition is based on the ability to mount IgE responses to common allergens. Traditionally, the atopic state has been linked to chronic respiratory diseases in infancy and adolescence, and much less importance has been given to the atopic features in the more advanced age groups. This derives from the initial observations in geriatric populations that promoted the concept that atopy decreases with age.

Aging is associated with modifications of the immune system, defined as immunosenescence. A well-described feature of immunosenescence is the reduction in the size of the hematopoietic compartment of bone marrow with increasing age and its replacement by fatty adipose tissue [1]. Current studies implicate aging-induced dysregulation of cytokine and hormone networks with a loss in bone marrow stem cell output across the lifespan [2,3]. Aged bone marrow-resident macrophages have shown a decreased ability to secrete TNF, which in turn modulates

the production of other cytokines, such as IL-6, IL-11, macrophage colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. Taken together, these observations suggest that the composition of bone marrow stroma and its ability to nurture hematopoietic precursors is substantially compromised with aging. The thymic epithelial space, in which thymopoiesis occurs, makes up less than 10% of the total thymus by 70 years of age. Age-associated architectural changes also occur in secondary lymphoid tissues. Studies performed in elderly subjects revealed a decline in the paracortical and medullary zones of the lymph nodes, an increase in adipose tissue and less evidence of germinal center formation [4].

The characteristics of lymphocytes in the spleen and lymph nodes change significantly with age. Peripheral B-cell numbers do not decline with age, but a lower antibody response, a decreased ability to produce high-affinity antibodies and reduced IgG isotype class-switching are present [5]. Aged CD4⁺ T cells have decreased CD40 ligand (CD40L) [6], a critical stimulatory ligand for T cell–B cell interactions [7]. Haynes

and Eaton suggested that impaired T cell–B cell interactions due to decreased IL-2 production by aged T cells contribute to the impaired humoral (B-cell) responses in older individuals [8].

In addition, attenuation of dendritic cell (DC) function is observed with increasing age [9]. Different subsets of DCs, such as myeloid DCs, plasmacytoid DCs and those present in the tissues/organs, exist. The behavior of these cells can be studied using monocyte-derived DCs (MODCs). They are generated *in vitro* from monocytes in the presence of granulocyte-macrophage colony-stimulating factor and IL-4 and are closely related to interstitial DCs. Agrawal *et al.* reported that peripheral blood DCs and MODCs are similar in young and aged subjects, and generation of MODCs from peripheral blood monocytes is comparable between young and aged subjects [10]. However, MODCs migration, micropinocytosis, and receptor-dependent and -independent phagocytosis are impaired in older adults.

There is also a considerable difference in hematopoietic activity in adults and the elderly. Studies on the frequency of proliferative capacity of a colony-forming unit of granulocytes and macrophages in bone marrow of different ages show a functional decline in stem cell precursors that begins at birth and continues throughout life [11]. However, the hematopoietic potential is preserved in the elderly under basal condition (steady state) and it is only the capacity of stem cell renewal after hematological stress that declines gradually with advancing age. Thus, in the absence of stress conditions, the absolute numbers of eosinophils and basophils in young versus older adults remain quite similar [12].

It should be mentioned that the phenomenon of immunosenescence is not homogeneous; indeed, an interesting aspect of immunosenescence, described as ‘inflammaging’, is proposed to describe the global reduction in the capacity to cope with a variety of stressors [3]. This process is provoked by continuous antigenic load and stress, and antigens are considered another type of stressor. It follows that a progressive increase in the proinflammatory status occurs. In the elderly, the cytokine secretion pattern shifts towards that dominated by type 2 cytokines, thus inducing an imbalance between Th1 and Th2 responses with aging. One of the causes of the increased inflammation seen in aging could be related to the increased level of IL-6, which promotes the Th2 response. The clinical significance of the increased Th2 response remains to be determined. A powerful Th2 response suppresses the Th1 response, and the subject becomes potentially more susceptible to infections. On the other hand, because of the predominance of Th2 responses, an increased prevalence of allergic conditions could be observed in these patients. However, further studies are required to elucidate the functional and clinical consequences of the imbalance between Th1 and Th2 responses in the elderly.

Asthma and the atopic condition are not expected to recover with aging. In addition, senescence-associated limitations in functioning and in local and systemic defenses, along with long-term exposure to environmental noxious stimuli and allergens, expose the elderly asthmatic to the risk of more frequent and more intense attacks. The burden of senile asthma must be weighed in the perspective of the progressive aging of the population, whereby the current number of people aged 60 years and over is expected to double by 2025. Taken

together, these observations lead us to postulate that asthma in the elderly will markedly increase its impact on public health in the coming years. Despite these considerations, asthma in the elderly is still underdiagnosed and undertreated. Studies from Europe, the USA and Australia confirmed that the diagnosis of asthma is often missed in older patients. It follows that underdiagnosis of asthma in the elderly is a worldwide problem [13–15]. Nowadays, the data regarding the prevalence of asthma in the elderly are not homogeneous, with large differences between countries. Several reasons could be advocated to explain the discrepancies in the prevalence rates, including genetics, climate conditions, and exposure to allergens or environmental and pollutant agents. It is worthwhile to underline that the studies that addressed the prevalence of asthma in the elderly differ in terms of the age range used to define the geriatric state. This would greatly affect the prevalence of the disease. Similarly, the different prevalence of asthma in the elderly depends on the diagnostic criteria used to describe the disease.

The current article aims to examine the role of atopy in elderly patients as it pertains to the diagnosis, therapy (adoption of preventive measure such as removal of environmental allergen or immunotherapy) and prognosis (influence on morbidity and mortality) of chronic respiratory illnesses.

Methods

To assess the impact of age on atopy, a literature search using MEDLINE for the years 1966–2010 was performed. The search included the medical subject headings terms ‘aged’, ‘atopy’, ‘allergy’, ‘allergen’ and ‘IgE’; since ‘aged’ identifies subjects aged between 65 and 79 years, the string ‘aged 80 and over’ was added. The search was restricted to human studies and articles published in English. In addition to extracting information on the design of each study, we recorded the method applied to assess the atopic status (serum-specific IgE or skin-prick test) and the characteristics of the studied population (healthy people, asthmatics and/or rhinitics). We excluded articles that used total IgE levels as a descriptor of atopy, because this end point is known to be influenced by various factors, such as smoking habit, gender, environmental exposure and parasitic infections, which could confound the outcomes of the current article. The literature search led to the selection of articles that allowed us to speculate on the clinical implications of atopy in the elderly population. To this aim, we focused on the role of atopy in the occurrence of airway hyperresponsiveness (AHR) and asthmatic symptoms in the process of distinguishing asthma from other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD), and in the topic of treatment of asthma in the elderly.

Clinical implications of atopy in the elderly

Airway hyperresponsiveness

Several studies performed in adolescent or adult populations have confirmed the close relationship between atopy and AHR [16,17]. For example, Witt and colleagues observed that the prevalence of AHR, assessed by histamine bronchoprovocation, in children and in adults increases proportionally with the number of sensitizations, assessed by allergen skin testing [18].

Our group has previously reviewed the relationship between aging and AHR [19]. Several studies indicate a bimodal distribution in the general population across ages, with the highest susceptibility in the early and late phases of life [20,21]. However, other studies have found a lower prevalence of AHR in the most advanced ages [22,23]. Regardless of this controversy, AHR is far more common among the elderly than previously recognized, with prevalence rates ranging from 29 to 43%. Major factors contributing to the high prevalence of AHR in older adults are structural and physiological modifications of the lung [24,25]. Atopy may also be an independent predictor of AHR in the elderly, based on our review of the existing literature [19]. For example, in a study conducted on a male population with an average age of 64 years, a significant relationship between AHR and specific serum IgE levels against *Dermatophagoides* was identified [26].

The clinical significance of AHR in older adults should be emphasized. In the geriatric respiratory patient, AHR is associated with a more rapid decline in pulmonary function and a greater risk of clinical exacerbations, establishing AHR as an independent risk factor for mortality [27]. In addition, since asthma in the elderly is often underdiagnosed or misdiagnosed [28,29], detecting AHR could be helpful in the differential diagnosis of asthma in these individuals. Given the relationship between atopy and AHR, evaluation of atopy may help identify high-risk patients.

Asthmatic symptoms

Asthma is a frequent disease among older individuals, affecting approximately 4–8% of those above the age of 65 years [30]. Asthma in the elderly can be distinguished in terms of early- or late-onset. Atopy seems to be more frequent in patients with early-onset asthma than in those with late-onset asthma. Furthermore, it is generally believed that true allergic asthma very seldom starts in old age and that, in this case, it is intrinsic asthma (i.e., without any sensitization to aeroallergens). In a retrospective study, Bauer *et al.* demonstrated that in 98 Rochester (MN, USA) residents with onset of asthma at, or after, 65 years of age, only 11% had positive allergen skin tests [31]. It is still unclear, however, whether allergic exposure and sensitization play the same role in the development of disease in adults as they do in children. The prevalence of elevated IgE levels is lower among those aged over 55 years of age than in younger patients, and late-onset asthma is often mistaken for COPD. As a consequence, late-onset asthma is also inadequately treated [32].

Currently, the role of atopy in the late-onset asthmatic patient is still unclear. Burrows *et al.* evaluated 40 elderly subjects who denied ever having asthma or emphysema on enrollment in a longitudinal epidemiologic study [33]. The average age at which the diagnosis of late-onset asthma was reported was 70.8 years, after a mean follow-up of 8.5 years. Findings on enrollment in the late-onset asthma patients were compared with findings in the 1145 subjects who provided follow-up information when they were older than 60 years of age but had never developed asthma. In total, 35% of the late-onset asthmatics recalled 'respiratory trouble before age 16' despite denying prior asthma. This finding underlines that symptoms suggesting asthma are usually present for many years before the diagnosis of the disease in elderly

subjects. Moreover, the authors found that atopy is implicated in the pathogenesis of late-onset asthma. Indeed, the likelihood of a new diagnosis of asthma was very closely related to the age- and sex-standardized serum IgE level before diagnosis.

On this basis, it is plausible that atopy also plays a role as predictor of asthma in the geriatric age group. In this regard, Parameswaran and colleagues evaluated different possible predictors of asthma (such as severity of airflow limitation, history of childhood wheeze, duration of wheezing, smoking history, indoor heating, sex, atopy history and numbers of puffs of salbutamol per day) in an elderly asthmatic population [34]. Of all the factors, the authors found that history of atopy was the strongest predictor of asthma in the elderly population.

Ariano *et al.* compared the role of atopy in asthmatics who belonged to different age groups [32]. The diagnosis of atopy was assessed in 21 late-onset asthmatic patients over 65 years of age using total IgE, skin-prick tests and radioallergosorbent tests for the most common allergens of Northern Italy. This group was compared with three groups of age-matched subjects consisting of 68 patients affected by chronic bronchitis, 14 patients who had asthma before the age of 65 years (presenile asthma) and 20 healthy controls. A group of 15 asthmatics under the age of 65 years was also included. Although age (except in the young asthma group) and severity of symptoms were similar in the four groups, the level of specific IgE and skin test positive responses were unexpectedly higher in late-onset asthma than in young and presenile asthmatics. This is in contrast with the results of other studies [30,35]; nevertheless, the authors claimed that atopy is common among late-onset asthmatics.

In general, older patients complain less about asthma symptoms, and this is especially true in patients with long-standing disease. When younger patients with asthma were compared with older patients who either developed asthma in older age (>65 years) or acquired the disease when they were younger (<65 years), the group of elderly subjects with early-onset and long-standing asthma showed more severe disease in terms of clinical features and functional characteristics than the other two groups [36].

In children with respiratory symptoms, the severity of symptoms has been associated not only with the degree of bronchial obstruction but also with the magnitude of allergic sensitization [37]. Despite the alleged lower prevalence of allergic sensitizations in the elderly, the question is whether atopy *per se* affects the asthmatic phenotype in this population. Asero investigated the effects of exposure to allergens on a sample of 2571 individuals living in Northern Italy [38]. The author found a higher incidence of respiratory diseases in elderly subjects with positive skin test and family history for allergic diseases. A case-control study was conducted in older men from the Normative Aging Study to address the role of the allergic response to environmental aeroallergens in the development of asthma [39]. A total of 33 elderly subjects who developed new-onset airway hyperresponsiveness on methacholine challenge testing were compared with 66 age-matched controls who maintained normal methacholine challenge tests. The hyperreactive individuals had a higher prevalence of serum IgE reactivity to cat allergen (18.2 vs 6.1%) and *Dermatophagoides* (21.2 vs 10.6%) measured in serum obtained 3 years before the

development of airway hyperresponsiveness. The authors found a significant association between indoor allergen sensitization and the occurrence of asthmatic symptoms.

Asthma versus COPD

Another aspect of the assessment of atopy in the elderly is related to its possible role in the differential diagnosis between asthma and COPD in the geriatric patient. Indeed, if, on one hand, asthma maintains its basic clinical characteristics in the elderly, and on the other hand, features of COPD develop as the patient ages, the differences in terms of clinical and functional manifestations between these two conditions become less evident. The attenuation of reversibility of bronchial obstruction in older adults both by physiologic mechanisms (lung inflation) [40] and by bronchodilators [41], the history of smoke exposure and the low perception of symptoms complicate the clinical phenotype of the elderly asthmatic subject. In this context, some authors have proposed the evaluation of atopy as a useful tool in the differential diagnosis between asthma and COPD in the elderly [42]. However, this matter has not been investigated thoroughly and current guidelines do not include the assessment of the allergic component to distinguish asthma from COPD [43]. The major problem is that atopic individuals may develop COPD because of environmental exposures or because of intrinsic susceptibility, without asthma being part of their pathology. On the other hand, it is now well recognized that the lower airways of almost all atopic individuals are inflamed and/or show evidence of subclinical physiologic abnormalities [44].

Asthma versus other chronic respiratory diseases

The association between asthma and other diseases of the upper and lower respiratory tract deserves some attention. There is a high prevalence of lower airway disease in patients with chronic rhinosinusitis. In a prospective study, adult patients with chronic rhinosinusitis were assessed with functional and imaging procedures [45]. Approximately a third of patients presented with lower airway diseases, suggesting a contributing role of upper respiratory tract diseases in the occurrence of asthma. The coexistence of bronchiectasis and asthma has been seen in many patients. In a large sample of asthmatics, Oguzulgen and colleagues identified a subgroup of patient with bronchiectasis who were compared with another group of age- and gender-matched asthmatics without bronchiectasis [46]. Asthmatics with bronchiectasis had more severe asthma, a history of more frequent hospitalizations due to severe asthma exacerbation and more frequent presence of chronic respiratory failure. The relationship between bronchiectasis and asthma in elderly patients needs to be elucidated further. In this complex scenario, the coexistence of atopy could help in differentiating asthma from the other conditions.

Asthma management

The identification of an allergic component of asthma in the elderly patient may influence treatment. First, the recognition of allergens as possibly responsible for the respiratory condition allows preventive environmental strategies to be applied. Older individuals spend more time in the same indoor environment compared with

younger adults, and it is conceivable that the impact of environmental control, particularly for indoor allergens (mites, molds, pets and cockroaches) will be higher in this age group. However, no published study has addressed this hypothesis. Second, with the advent of better or easier to use methods of immunomodulation for allergy treatment (e.g., allergen-specific subcutaneous immunotherapy using effective adjuvants to increase the immune response while reducing the risk of systemic reactions, sublingual immunotherapy and anti-IgE treatment), elderly patients may be managed more effectively. Immunotherapy should be considered in elderly individuals with specific indications [47]. Indeed, age *per se* does not preclude the use of allergen desensitization, as demonstrated by Asero [48], who confirmed the efficacy of injection immunotherapy with birch and ragweed pollen extract in elderly individuals. However, owing to the frequent occurrence of comorbid conditions and the use of concomitant medications that could interfere with the immunotherapy, risks and benefits should be carefully evaluated in the elderly. For example, patients receiving β -adrenergic blocking drugs are at an increased risk when receiving allergen immunotherapy because blockade of β -receptors can render the treatment of anaphylaxis more difficult. In these cases, immunotherapy should not be initiated unless the benefits and risks are considered and discussed with the patient.

The identification of an allergic component may also influence the control of the disease. In this context, anti-IgE therapy is the newest available therapy for atopic asthma [49]. Omalizumab is a monoclonal antibody that selectively binds to human IgE. This drug is delivered subcutaneously every 2–4 weeks, and this may represent a limitation for some elderly patients, who often need assistance to reach the outpatient clinic. The use of omalizumab in older people with allergic asthma has been evaluated in a pooled analysis that showed a reduction of the risk of exacerbations, improvement of asthma symptom scores and reduction of rescue medication use in adults aged over 50 years with moderate-to-severe allergic asthma [50].

Expert commentary

Allergies have been traditionally considered conditions affecting children and young or even middle-aged adults. The immune system undergoes an involution process with a consequent decline in immunoglobulin production, including IgE. This has led us to consider asthma in the elderly a disease of nonallergic pathogenesis. As a consequence, atopy has been relegated to a minor role in the clinical assessment of the geriatric respiratory patient. This concept has probably contributed to underdiagnosis of asthma in the elderly. This can have clinical consequences because management may suffer; it may also have a substantial impact on direct and indirect public health costs. The notion that asthma exists in the elderly has only gained significant ground among physicians in the last few decades. Today, asthma in the elderly is a well-recognized condition, with unique features reflecting the coexistence of other diseases, the use of multiple respiratory and nonrespiratory drugs, individual responsiveness to treatment and different perception of symptoms. Although available data seem to favor the decline of allergen sensitization with age, these data have not

been optimally collected. Even if these data were acceptable, the prevalence of allergic sensitizations in the elderly population with respiratory symptoms is substantial enough to warrant evaluation of the atopic condition. This approach will improve diagnosis and could allow the introduction of allergy-specific management, leading to a significant reduction in asthma morbidity.

Five-year view

The title of the current article is challenging for clinicians and researchers. Indeed, atopy and allergic asthma are usually confined to the young decades. Therefore, a clear-cut response to the question posed by the title becomes a difficult task. In our work, we have made an effort to identify those articles that, by specifically addressing the question, can contribute to clarifying the issue of the role of atopy in elderly individuals. Based on the studies that were selected and included in the current article, we can claim that the evaluation of the atopic condition in the geriatric age group represents an additional tool in the diagnostic process and, consequently, in the therapeutic approach.

In the coming years, we hope to see more studies designed and performed to better describe late-onset asthma. We believe that it is necessary to conduct clinical studies in which researchers focus on the different aspects of this type of asthma, such as the

role of atopy in the pathogenesis, as well as in the clinical features of asthma in elderly patients as opposed to young subjects. We also believe that it is worth designing longitudinal studies in order to demonstrate whether it is possible (and how) to prevent the allergic late-onset asthma in a specific risk population (e.g., allergic rhinitis patients). Different forms of immunotherapy should be further evaluated in elderly allergic subjects, with regard to the prevention of asthma, the reduction of allergic symptoms and the decrease in allergic medication intake.

Over the next 5 years, we envision the design of large multicenter clinical trials that will allow us to decide whether and when the geriatric population should benefit from anti-IgE therapy. By acquiring further evidence, more asthmatic patients will be able to obtain advantages from this biological treatment, especially those with the most severe and poorly controlled asthma.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Aging is associated with modifications of the immune system (immunosenescence), and this could contribute to a reduced prevalence of allergic disease in the elderly. Although available data seem to favor the decline of allergen sensitization with age, the prevalence of allergic sensitizations in the elderly population with respiratory symptoms is substantial enough to warrant evaluation of the atopic condition.
- Allergic asthma is less commonly recognized as a geriatric respiratory disease due to a cultural bias that associates it with childhood and adolescence. By contrast, asthma is a frequent condition among older individuals, affecting approximately 4–8% of those above 65 years of age.
- Atopy is important in elderly subjects in that it acts as an independent predictor of asthma. It is more frequent in patients with early-onset asthma than in those with late-onset asthma.
- A significant association between indoor allergen sensitization and the occurrence of asthmatic symptoms in the elderly patient has been documented.
- Immunotherapy should be considered in elderly individuals with specific indications, provided that the occurrence of comorbid conditions and the use of concomitant medications that could interfere with the immunotherapy have been excluded.

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