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REVIEW

The impact of age on prevalence of positive skin prick tests and specific IgE tests

Nicola Scichilone [a,*], Adriana Callari [a], Giuseppe Augugliaro [a], Margherita Marchese [a], Alkis Togias [b], Vincenzo Bellia [a]

[a] *Dipartimento Biomedico di Medicina Interna e Specialistica (DIBIMIS), Sezione di Pneumologia, University of Palermo, "Villa Sofia-Cervello" Hospital, Palermo, Italy*
[b] *NIAD/NIH, Bethesda, MD, USA*

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Summary
Aging is associated with modifications of the immune system, defined as *immunosenescence*. This could contribute to a reduced prevalence of allergic disease in the elderly population. In this regard, 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 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. Unfortunately, no large, longitudinal studies performed in the general population have been conducted to further explore 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. From a clinical perspective, allergic reactions in older adults can have the same or even worse manifestations compared to young people. For this reasons, the evaluation of the atopic condition also in the geriatric patient is recommended. Thus, the role of atopy 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 in the elderly is addressed.

* Corresponding author. Department of Internal Medicine, Division of Pulmonology (DIBIMIS), University of Palermo, "Villa Sofia-Cervello" Hospital, Via Trabucco 180, 90146 Palermo, Italy. Tel.: +39 091 6802646; fax: +39 091 6882165.
E-mail address: n.scichilone@libero.it (N. Scichilone).

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Introduction

Over the past several decades, the elderly population has steadily increased because of longer average lifetime. Aging is characterized by a progressive decline of the function of various systems and organs. As a result, the mechanisms of chronic diseases are often influenced by pathophysiological consequences of age-related changes. Aging is associated with modifications of the immune system, defined as *immunosenescence*.[1–7] The size of the hematopoietic compartment of bone marrow decreases with increasing age and is replaced by fatty adipose tissue, implying that the composition of bone marrow stroma and its ability to nurture hematopoietic precursors is substantially compromised with aging. 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 stressing conditions, the absolute numbers of eosinophils and basophils in young versus older adults remain quite similar. Age-associated architectural changes also occur in secondary lymphoid tissues. 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 and a decreased ability to produce high affinity antibodies are observed. This suggests impaired humoral (B cell) responses in older persons. In addition, attenuation of dendritic cell function is observed with increasing age. As it will be discussed, the link between age-associated modifications in the immune system and the skin test positivity is yet to be demonstrated.

Asthma is not a rare entity in the elderly population. In studies performed in the UK, asthma prevalence in the elderly ranged from 2.5% to 6.5%.[8–10] A survey study published in 2005 found that asthma in elderly Hispanic and non-Hispanic white population of Texas, USA[11] had a prevalence of 6.3% (current asthma) and 9.0% (probable asthma). The contribution of atopy in the occurrence of asthma in the elderly has not been properly established. The current review aims at evaluating whether atopy, as assessed by specific serum IgE, or skin reactivity to aeroallergens, is influenced by the aging process.

Methods

To record our current knowledge on the impact of age on atopy, a systematic literature search using MEDLINE for the years 1966—2010 was performed. The algorithm of the methodology that was applied included the term "aged", as MeSH (Medical Subject Headings) term together with "atopy", "allergy", "allergen" and "IgE"; since "aged" identifies subjects aged between 65 and 79, the string "aged, 80 and over" was added. Studies performed only in young adult and children populations were excluded. The search was restricted to human studies and articles published in English language. All articles that were identified were examined for eligibility by some of the authors (NS, AC, GA and MM), and disagreements were discussed with the remaining authors; articles were accepted for further evaluation by consensus. In addition to extracting information on the design of each study, we recorded the method applied to assess the atopic status (serum specific IgE, 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 endpoint is known to be influenced by various factors, such as smoking habit, gender, environmental exposure, parasitic infections, which could confound the outcomes of the current review.

The majority of studies were of cross-sectional design. Moreover, the evaluation of the atopic status in many studies was performed without discriminating between specific IgE levels and the response to allergen skin prick test (SPT), or between healthy and atopic subjects or subjects with chronic respiratory diseases. This must be taken into account when comparing different studies. We did not apply any age limit, but we ensured that extreme ages were incorporated.

Because of the restrictive criteria used in the current review, only 16 studies were included in the analysis. Table 1 summarizes the main characteristics (sample size, age range, atopy, sample features, and the effect of age on atopy).

Table 1 List of the studies included in the current review. The main characteristics for each study are depicted. sIgE: serum specific IgE.

Author (date)	Sample size	Age	Atopy Outcomes	Sample features	Effect of age on atopy outcome
Gergen et al. 1987	16204	12—74	Prick test	Healthy	Decreased with age
Wuthrich et al. (1996)	8344	18—60	sIgE Prick test	Healthy	Decreased with age
Kerkhof et al. (2003)	2327	20—70	sIgE Prick test	Healthy	Decreased with age
Sapingi et al. (1998)	1905	8—73	Prick test	Healthy	Decreased with age
Nakazawa et al. (1994)	1049	18—99	sIgE	Healthy	Decreased with age
Barbee et al. (1981)	311	9—65	sIgE Prick test	Healthy	Decreased with age
Barbee et al. (1981)	2743	6—90	sIgE	Healthy	Decreased with age
Freidhoff et al. (1984)	320	20—60	Prick test	Healthy	Decreased with age
Hanneuse et al. (1978)	326	16—69	sIgE	Atopics	Decreased with age
Karakaya et al. (2006)	222	17—68	Prick test	Asthmatics and/or rhinitics	Decreased with age
Niemeijer et al. (1992)	499	4—75	Prick test	Asthmatics	Decreased with age
Eriksson et al. (1996)	7099	14-70	Prick test	Asthmatics and/or rhinitics	Decreased with age
Mitsunobu et al. (2000)	263	31—90	sIgE	Asthmatics	Decreased with age
Hsu et al. (2004)	504	<15—64+	sIgE	Asthmatics	Decreased with age
Stoy et al. (1981)	331	n.d	sIgE Prick test	Asthmatics and Healthy	Decreased with age
Huss et al. (2001)	80	>65	Prick test	Asthmatics	Increased with age
Crawford et al. (2004)	132	25—75	Prick test	Asthmatics and/or rhinitics	Increased with age

Results

Atopy decreases with aging

Several studies have found decreasing prevalence of atopy with age either in general population samples or in population samples of healthy, i.e. with no allergy-related symptoms, humans. The National Health And Nutrition Examination Survey (NHANES) II is the largest prick puncture skin study reported, including a total of 16204 participants from the non institutionalized US population, who were skin prick tested to eight allergens. Some 30% of individuals aged 12—24 years had at least one positive skin test; the prevalence of positive response dropped to 8% in the group of subjects aged 65—74.[12] In another analysis performed in a total of 8179 subjects from the NHANES population, aged between 30 and 75 years, the authors demonstrated a reduction in the prevalence of positive skin responses with increasing age.[13] An important contribution to the relationship between age and atopy derives from the results of the SAPALDIA study.[14] In this large, cross-sectional study of healthy subjects (18—60 yrs), atopy was evaluated in relation to age, gender and smoke habit. The study documented a reduced prevalence of atopy in the most advanced ages: the prevalence of allergen-specific IgE antibody concentrations, positive prick tests and allergic manifestations decreased significantly by 23%, 21% and 21% respectively, with every 10-year increment in age. The lower prevalence of atopy in older subjects was also documented in a Dutch general population study,[15] which was performed with the aim of identifying cut-off values of total IgE to discriminate between subjects with and without sensitizations to common aeroallergens. In order to create receiver operator characteristic curves, at least one positive SPT or specific IgE levels against at least one allergen served as "gold standard" for sensitization. The study sample included subjects aged 20—70 years, and was stratified in two age groups (20—44 and 45—70 years). The authors found a significantly higher number of subjects with at least one positive SPT or specific IgE levels against at least one allergen in the 20—44 year group as opposed to the 45—70 year group, both in subjects with allergy symptoms and those with no symptoms. Similar findings were documented in a stratified population sample of 8—73 year-old individuals.[16] In another study carried out in a general healthy population (age range: 18—99 yrs), specific IgE antibodies to mites and Japanese cedar pollen were found to be lower in the most advanced ages. In particular, the percentage of subjects who were positive for anti-mite antibodies decreased from 27% in the young group to 15% in the older group, and even more in the over 70 year group.[17] By testing the sensitivity to the most common aeroallergens in a community population sample, Barbee and colleagues[18,19] found the highest prevalence of positive SPT in subjects ranging 6—14 yrs and 20—34 yrs, and the lowest prevalence in women older than 75 yrs. Also, Freidhoff and colleagues[20] demonstrated a tendency of SPT positivity to decrease between 20 and 60 yrs of age in a random sample of 320 adults.

Similar findings were obtained when the relationship between atopy and age was assessed in individuals affected by allergic respiratory diseases. This was first reported in 1978 by Hanneuse and colleagues,[21] in 326 allergic patients, in whom specific IgE levels to the most common aeroallergens were found to be significantly lower in the older subjects. In a prospective study,[22] specifically designed to determine possible changes in atopy over a follow-up period of a short period, 2 years, 222 asthmatics and rhinitics (age range: 17–68 yrs) were skin tested for common aeroallergens: repeat tests showed that the prevalence of positive SPT dropped from 58.6% to 47.7%, with the most important factor affecting this trend being time itself. In another investigation, the prevalence of skin test reactivity to at least one allergen was inversely correlated with age in an asthmatic population aging 4–75 yrs.[23] This was true for all the common aeroallergens tested, except for grass pollen. In yet another large study on asthmatics and/or rhinitics,[24] the prevalence of skin reactivity to allergens, equal to 44% for the entire study group, was found to decrease with age: the prevalence of positive SPT was 61% in the youngest group (14–20 yrs), and only 18% in the oldest (61–70 yrs). Another study performed in Japan supports this claim[25]; the population tested consisted of 263 asthmatics with average age of 60 (range 31–90). The specific IgE levels were significantly lower in the oldest subjects. Asthma and age were the main variables explored in a study performed in Taiwan[26]; 504 asthmatics were divided according to age of onset. Specific IgE levels were found to be lower in the oldest individuals, demonstrating that atopy is more prevalent in early onset than in late-onset asthma. Finally, the changes in specific IgE and SPT responses with age were evaluated in a total of 331 individuals consisting of asthmatics and healthy subjects.[27] Results demonstrated a tendency of specific IgE levels and SPT positivity to be lower in the most advanced ages in both groups.

Atopy does not decrease with aging

Among the studies that met the criteria for inclusion in the current review, only two showed a lack of decline in the prevalence of atopy with aging. However both studies have limitations. The prevalence of allergy in asthma in the elderly was determined in a study performed in Baltimore, USA[28]: in 80 asthmatics older than 65 years, 75% presented with at least one sensitization to common airborne allergens as assessed by SPT. The second study was a cross-sectional survey performed in adult asthmatics and rhinitics to assess the age effects on atopy.[29] The sample consisted of 132 individuals with mean age of 55 years, stratified according to age in six groups (25–34, 35–44, 45–54, 55–64, 65–74). The prevalence of positive SPT was similar among the age groups in the subgroup of asthmatics (71 subjects). The small number of subjects in this study precludes any meaningful conclusion.

Discussion

The findings of our review are consistent with the notion that the prevalence of allergic sensitization is lower in the most advanced ages. Unfortunately, no large, longitudinal studies among the general population have been conducted to confirm that atopy decreases with increasing ages. This is a major deficiency, because a significant caveat of cross-sectional studies in this field is that a lower prevalence of atopy in older groups may simply reflect a lower prevalence of atopy in the same individuals when they were young and not a reduction in atopic status with age. This should be seriously considered given the fact that atopy primarily develops in childhood and that the overall prevalence of atopy has been steadily increasing.[30] Law and colleagues published an interesting observation that supports the above possibility.[31] They measured specific IgE in stored serum samples of all men attending a general medical clinic in 1996-98 and compared the results to age- and month of attendance-matched samples of men that were seen in the same clinic in 1981-82 and in 1975–76. Their results indicated a steady increase in the percentage of Phadiatop® positive samples between the 3 cross-sectional evaluations. However, when they compared the results from those 3 testing periods for men born in 1932–42, no difference in the prevalence of atopy was detected. These results suggest that the prevalence of atopy may not decline with increasing age and that more recent cohorts are more likely to have atopy.

Limitations of the current review

The literature review that we conducted has limitations. First, atopy is not evaluated in a consistent manner across studies in that increased total IgE levels or positive SPT responses to allergens are used interchangeably. The level of total IgE is influenced by independent factors such as gender, smoke habit, parasitic infections, environmental exposure to allergens and number of sensitizations. As a result, we do not believe that total IgE concentration is the most appropriate clinical test to determine atopy. Hence, we selected only those studies in which atopy was defined by means of specific IgE concentrations toward aeroallergens and/or SPT positivity to at least one aeroallergen. This drastically limited the number of available publications for review. Second, several studies examining the effect of age on atopy suffer from small samples and/or narrow age range; these two parameters are pivotal in allowing reliable conclusions to be drawn. For example, the majority of studies which conclude that atopy does not change with age had to be disregarded in this review because of relatively small number of study subjects, as judged by the authors. Finally, the current review does not judge the fact that the oldest studies may have used not-standardized allergen extracts, which could have influenced the measurements of the indicators of atopy. This is a common issue that should be kept in mind when interpreting the results. On the basis of different designs and methods for estimation of sensitization, and the possible influence of the change in the last decades in the frequency of sensitization in children, adolescents and young adults, no firm conclusion can be drawn on whether there is a decreased sensitization rate in elderly healthy and allergic populations.

The prevalence of allergic respiratory diseases in the elderly

With the ambiguity of the question whether atopy decreases in older age aside, our review indicates that the point prevalence of allergic respiratory disease remains high in older adults. In Law's study, Phadiatop® positivity was approximately 35% in men 54–64 years of age.[31] Among a population of 1888 individuals over 65 years of age, Ariano and colleagues[32] recognized 21 subjects with asthma, who had high prevalence (72%) of skin reactivity for *dermatophagoides*, *parietaria*, grasses, and olive in individuals with late-onset asthma. Also, in a retrospective analysis of 1002 allergic asthmatics and/or rhinitics aged 8–77 years from our Outpatient Allergy Clinic (unpublished observations), the number of sensitizations did not change with age; indeed, the average number was 2.74 ± 1.5 (mean $\pm$ SD) in the 274 subjects with age <24 years (25° percentile), 2.71 ± 1.6 in the 488 subjects with age between 25 and 44 years (25°–75° percentile), and 2.53 ± 1.5 in the 240 subjects aged between 44 and 77 years (75° percentile) (ANOVA: $p = 0.25$).

The natural course of allergy is based on persistent antigen exposure; the repeated stimulation with identical antigenic proteins induces on one hand the expression of new surface molecules and, on the other hand, the expansion of effector and memory cells. It follows that, with aging, the number of naive cells decreases and the sensitized cells increase. In allergic asthma there is a continuous stimulation of T lymphocytes by several aeroallergens, which can lead to a decrease in naive T cells. Additional factors that have not been considered in the context of the effect of age on allergy are all the inflammatory events downstream from IgE. These include mast cell and basophil mediator releasability, which determines the quantity of inflammatory mediators released for a given magnitude of IgE receptor bridging, the responsiveness of other inflammatory cells to the chemoattractive and activating signals of mast cell and basophil mediators, as well as the responsiveness of target organs (e.g. vasculature, airway smooth muscle, glandular apparatus) to the effects of mediators derived from allergy-activated cells. Furthermore, the ability of the immune system to downregulate an ongoing inflammatory response needs to be taken into account.

The clinical importance of allergy in the elderly

Given that the above-described functions have not been studied in older adults in comparison to younger populations, it would be very hard to argue that an age-related reduction in the production of IgE, if real, diminishes the clinical importance of allergy in the elderly. In other words, despite a decreased prevalence of atopy, the severity of allergic conditions may be increased in older age. It has been suggested, for example, that the highest risk for asthma hospitalization derives from a combination of atopy and viral infections.[33,34] Although, again, the role of viral infections in conjunction with atopic status has not been studied in the elderly, alterations of immune responses could increase susceptibility to infection, which, in turn, could amplify the inflammatory response and the synergism between atopic status and viral infections in asthma in this population. Atopy appears to be more frequent in elderly patients with early onset than in those with late-onset asthma. Parameswaran and colleagues[35] found that history of atopy was the strongest predictor of asthma in the elderly population. 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, but 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),[36] and by bronchodilators,[37] 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.[38] However, this matter has not been investigated thoroughly and current guidelines[39] do not include the assessment of the allergic component to distinguish asthma from COPD. 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.[40]

Allergic reactions in older adults, when taking place, can have the same or even worse manifestations, compared to younger people, given the fact that various systems and organs, the function of which is also in decline, may not be able to compensate. Theoretically, for the same degree of a systemic anaphylactic reaction, the compensation that the cardiovascular system can mount in a young allergic individual is expected to be much more effective than that in an older person. In addition, as mentioned previously, known interactions between allergy and other conditions (primarily viral, but also bacterial infections, pollutant-induced oxidative stress, etc.) may be potentiated in the elderly in a manner that results in more severe manifestations of allergic respiratory disease. Finally, the severity of allergy-related attacks in the elderly may be influenced by the low perception of symptoms[41] and by the common presence of comorbidities[42,43] that may interact with and increase the side-effects or decrease the effectiveness of conventional allergy and asthma treatment. Therefore, allergy diagnosis and management should be considered in all upper and lower respiratory diseases in the elderly.

Regardless of age, assessment of atopy is essential in a comprehensive evaluation of the respiratory patient offering the possibility of environmental control (removal of allergens) and appropriate therapy (e.g., anti-IgE or allergen immunotherapy). This is particularly important based on the prevalence of asthma in the elderly populations.[11] Atopy may be an independent predictor of airway hyperresponsiveness in the elderly, based on our review of the existing literature.[44] This is of great

importance, given that in the respiratory geriatric patient, airway hyperresponsiveness is associated with a more rapid decline in pulmonary function and a greater risk of clinical exacerbations.[45]

Possible explanations for "false negative" skin test responses in the elderly

Criteria for interpreting skin test results differ between younger and older patients, and the incorrect interpretation of skin testing may lead to false negative responses. One possible explanation can be found in the age-associated reduction in skin reactivity of the elderly to histamine and allergens. Skassa-Brociek et al.[46] demonstrated a decrease in skin tests reactivity to histamine after 50 years of age, reaching a plateau after the age of 60. Moreover even if a wheal to histamine was reported in all subjects aged over 70 years, the flare was difficult to detect in a proportion of subjects. Thus, in geriatric age the intensity of the skin response should be expressed as the ratio between allergen and histamine induced wheals. In addition, the skin reactivity varies in the different body regions; in fact, as different studies have demonstrated,[47] the back is more reactive than the forearm, and this difference is greater for allergen than for histamine skin tests. Prior to performing a skin prick test in the elderly, the area of the skin should be examined for atrophic or photo changes, which may influence the response to allergens.[48] Indeed, the skin of older people undergoes atrophy that results in fewer cell layers and decreased cellularity and collagen. The marked reduction in blood vessels and mast cells offers less potential binding sites for allergen and less histamine to produce wheal and flare.[49,50] In the photo-damage of the skin, which is strictly related to the prolonged exposure to sun, the reason of a false negative response in skin prick test can be found in the role on mast cells, which are altered by solar damage.[51,52] Other factors could affect negatively the response to skin test in the elderly such as medications, especially antihistamines and antidepressants. Finally, the possibility exists that older subjects are no longer exposed to specific allergens they were positive to, and this may greatly reduce the skin test responses. A negative skin prick test cannot completely exclude the presence of an allergic condition. The concept of localized mucosal allergy in the absence of atopy has recently been proposed, with the existence of local allergic rhinitis with nasal production of specific IgE antibodies in the absence of atopy in over 40% of rhinitic subjects classified as non-allergic. This may further complicate the relationship between the presence of atopy in the geriatric age.[53,54]

The role of allergy in the management of asthma in the elderly

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 for preventive environmental strategies to be applied. Older individuals spend more time in the same indoor environment,[11] compared to younger adults and it is conceivable that the impact of environmental control, particularly for indoor allergens (mites, molds, pets, cockroach) 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. subcutaneous immunotherapy using effective adjuvants to increase the immune response while reducing the risk of systemic reactions, sublingual immunotherapy, anti-IgE treatment) elderly patients may be managed more effectively. Immunotheraphy should be considered in elderly individuals with specific indications.[55] Indeed, age per se does not preclude the use of allergen desensitization, as demonstrated by Asero,[56] who confirmed the efficacy of injection immunotherapy in elderly individuals. However, because of 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 beta-adrenergic blocking drugs are at increased risk when receiving allergen immunotherapy because treatment of anaphylaxis can be more difficult. In these cases, immunotherapy should not be initiated unless benefits and risks are considered and discussed with the patient.

Conclusions

The immune system undergoes an involution process with consequent decline in immunoglobulin production, including IgE. This has led to consider asthma in the elderly a disease of non-allergic pathogenesis. As a consequence, atopy has been relegated to a minor role in the clinical assessment of the geriatric 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 public health direct and indirect costs.[57] Today, asthma in the elderly is a well-recognized condition, with unique features reflecting the co-existence of other diseases, the use of multiple respiratory and non-respiratory drugs, individual responsiveness to treatment, and different perception of symptoms.[58] 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. This approach will improve diagnosis and could allow the introduction of allergy-specific management leading to significant reduction in asthma morbidity.

Conflict of interest

None.

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