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Role of Allergen Sensitization in Older Adults

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Abstract

There is a common perception among physicians and patients that allergic diseases are not relevant in older adults. There is recognition that both innate and adaptive immune functions decline with aging. It is the function of a variety of immune cells in the form of allergic inflammation that is a hallmark of allergic diseases. In fact, there is a fairly consistent observation that measures of allergic sensitization, such as skin prick testing, specific IgE or total IgE decline with age. Nonetheless, the association between allergic sensitization and allergic diseases, particularly asthma and allergic rhinitis, remains robust in the elderly population. Consequently, an appropriate evaluation of allergic sensitivities is warranted and indicated in older asthma and rhinitis patients in order to provide optimal care for the individual and minimize any resultant morbidity and mortality.

Introduction

During the 20th century, the elderly (over 65 year old) population in the US increased 11-fold and is expected to represent 20% of the US population by 2030 (US Census Bureau), mostly due to increased longevity. Given this change in age demographics in the US, greater resources are being channeled to understanding diseases impacting the elderly. Aging brings about a myriad of changes in all organ systems within our body, and the immune system is no exception.

The term “immunosenescence” has been coined to reflect age-related changes in the immune system,[1-3] which encompasses changes in both the numbers and/or functions of multiple cell types including T-cells, B-cells, NK cells, neutrophils, and eosinophils. There is literature demonstrating a deterioration in the function of both the adaptive[4,5] and innate[6] arms of the immune system rendering the elderly more susceptible to frequent infections, autoimmune disease, and malignancy.[7,8] These changes also have potential implications for the prevalence and severity of allergic diseases in the elderly. Atopy or allergic sensitization as measured by skin prick tests (SPT), allergen specific IgE and total IgE appears to decrease with aging. While this might provide us with some insight into the prevalence of atopy in an epidemiological sense, it should not deter us from pursuing an appropriate work-up for allergic causes in an individual patient. This is due to the fact that the relationship between the prevalence of positive allergen specific IgE or SPT or total IgE and allergic diseases such as asthma and allergic rhinitis remains robust even in elderly patients.[9-12] With an underlying impaired immune response noted with aging, it remains critical to identify elderly patients with allergic diseases to minimize mortality and morbidity. This review will first highlight some of the immunological changes associated

with aging, characterize the prevalence and clinical implications of allergic sensitization in the elderly, and finally discuss the role of atopy in asthma in the elderly.

Age Effects on Immune Function

Changes in the T-cell compartment with aging have been the most extensively evaluated component of the immune system. One of the most prominent changes is the involution of the thymus gland beginning with puberty and attaining completion by the sixth decade of life. Sansoni et al described an absolute age-related reduction in total T-cells (CD3+) involving both CD4+ and CD8+ subsets.[3] In addition, a decline in naïve T-cells (CD95-) and an expansion of memory (CD45RO+ CD28-) T-cells, particularly within the CD8+ subset, have been described. Memory cell responses and proliferative responses to antigens and mitogens are also diminished as well as T-cell receptor repertoire diversity.[13-15] And finally with aging, an increase in FOXP3+ CD4+ T-regulatory cells exerting suppressive effects on T-cell function along with a shift in cytokine pattern from T_H1 to T_H2 have also been described.[16,17]

Although peripheral B-cell numbers are unaffected with aging, there is a decline in the production of naïve B-cells from the bone marrow as demonstrated by flow cytometric assays.[18,19] In addition, there is also decreased diversification of B-cells[1], possibly due to impaired somatic hypermutation[20], in the germinal centers of peripheral lymphoid tissue where class switching and affinity maturation occur such that antibodies exhibiting lower affinity and avidity are produced leading to an overall “lower quality” antibody response.[21]

While a majority of neutrophil function including adhesion, migration, and phagocytosis remains intact, some aspects of neutrophil-mediated bacteriolysis are diminished in the elderly such as the ability to generate reactive oxygen species and kill phagocytosed organisms.[22-24] Increased apoptosis of neutrophils has been observed in the elderly owing to deficient cytokine-mediated signaling pathways that regulate neutrophil longevity.[25] Taken together, these changes result in decreased neutrophil-mediated response in acute inflammation and likely reflect more frequent and severe respiratory infections noted in the elderly.

Given its association with allergic diseases and asthma, eosinophils have also been examined in the elderly population. Increased peripheral blood eosinophils have been correlated with increased IL-6 levels in aged women from the Womens Health and Aging study.[26] No significant difference in sputum eosinophils were noted between older and younger asthmatic subjects.[27,28] From a functional standpoint, reduced eosinophil degranulation and production of superoxide in response to stimuli are observed in older asthma patients relative to young patients.[28] Since it has been proposed that eosinophil degranulation may have an anti-viral role,[29] the age-related decline in degranulation may contribute to more severe respiratory infections with viral etiologies. With regard to NK cells, their absolute number is increased with aging; however, their activity, cytotoxicity, proliferation and IFN- γ production in response to IL-2 are modestly diminished.[6] There is mixed evidence and discordance on the effects of aging on macrophages with regard to chemotaxis and phagocytosis. However, in mice and in vitro models, there is some consensus with regard to decreased proinflammatory cytokine production by macrophages and diminished ability for antigen presentation as evidenced by decreased expression of surface MHC II molecules.

Thus, with most immune cells, there appears to be compelling evidence for a decline in some functional aspect. However, the clinical impact of these changes is not well defined. In fact, many of the functional defects may actually result in exaggerated inflammation,

presumably as a compensatory response. This is often referred to as “inflamm-aging”, and is most notably associated with increased IL-6 and TNF- α levels in the serum.[30]

Atopy and Aging

Atopy refers to a hereditary predisposition towards the development of immediate hypersensitivity reactions to common environmental antigens and clinically manifests as allergic rhinoconjunctivitis, atopic dermatitis, asthma, or food allergy. Atopy is commonly assessed by measuring allergen specific IgE (i.e. RAST) or skin prick test (SPT) and occasionally by total serum IgE. These measures of atopy are often not evaluated in the geriatric patient due to a perception that allergy does not play a significant role in the elderly. Although there are data to suggest that measures of atopy decline with aging, the ultimate question is whether these measures have any clinical implications for the elderly.

Skin Prick Testing and Aging

Given its relative ease of administration and rapid results, the skin prick test is the most widely used means of assessment for atopy in all age groups. However, chronic skin changes (atrophy, photoaging, decline in mast cell numbers and vasculature) that occur as a result of aging and use of medications, particularly antihistamines, tricyclic antidepressants or selective serotonin reuptake inhibitors, can impact the results of the SPT. The earliest data on age effects on SPT results was published by Barbee et al in 1981 when they examined the prevalence of positive SPT to 14 common local antigens and total serum IgE.[31] They reported the lowest prevalence in females older than 75 with peak prevalence in the 20-34 year old age group. Another smaller study of 320 patients (age 20-60) also demonstrated a declining trend of positive SPT with increasing age.[32] The largest and most widely cited study on SPT is the National Health and Nutrition Examination Survey II (NHANES II) that included 16204 healthy patients in the US aged 6-74 who were tested by SPT to eight common allergens. Results revealed a reduction in prevalence of at least one positive SPT from 30% in the young (age 12-24) cohort to about 8% in the older (age 65-74) patients. Additional subgroup analysis revealed a decline from 22.3% (age 30-44) to 12.6% (age 60-75), $p < 0.0001$, in the prevalence of positive SPT with increasing age.[33] In another study of the general population in Italy by Baldacci et al, a higher prevalence of positive SPT, particularly to dust mites, was demonstrated in younger individuals with higher total serum IgE levels.[34] A very similar analysis of the same region conducted by Sapigni et al revealed that younger patients (8-14 years old) had the highest prevalence of SPT reactivity to house-dust mite and pollens and that a declining prevalence of positive SPT and total IgE exists with age.[35] With the use of SPT as a measure of atopy, there appears to be consistency in the finding that atopy declines with age. In addition, there are some data to suggest that this decline may be greater in females than males.

Allergen Specific IgE and Aging

Several studies have examined the prevalence of positive antigen specific IgE in elderly subjects. In many instances, it is the preferred means of atopy assessment in the elderly as the results are unaffected by skin changes that occur as a result of aging or concomitant medications. One of the first published studies to report on the effect of age on RAST and SPT results was by Stoy et al when they evaluated 331 (including 98 healthy non-atopic) patients to 6 common allergens (*Alternaria*, house dust mite, timothy grass, monilia, *Aspergillus*, and ragweed).[36] Their results showed a statistically significant decrease with age for *Alternaria*, house dust mite, and timothy grass with regard to SPT and RAST results, but not for the other three allergens. The Swiss SAPALDIA study is large cross-sectional study of 8344 healthy patients between the ages of 18 and 60 which was conducted to evaluate the influence of age, sex, and smoking habits on atopy.[37] The authors found that

the prevalence of allergen specific IgE, SPT, and allergic disease declined by 23%, 21% and 21% respectively with every 10-year increase in age. A decreasing prevalence of allergen specific IgE was also reported by Omenaas et al in their study evaluating 1512 patients (healthy and asthmatics) aged 18-73.[38] They noted a statistically significant decline in the prevalence of allergen specific IgE in four (timothy, birch, house dust mite, cat) of five allergens when comparing 55-73 year old patients versus 18-34 year old patients (adjusted OR of 0.1 to 0.2) with the only exception being mold where a decline was not noted. Nakazawa et al performed a similar analysis on 1049 healthy patients 18-99 years old to study the influence of aging on specific IgE production to Japanese cedar pollen(JCP) and mite allergen.[39] JCP-specific IgE was present in 30% of the 18-39 age group and declined to less than 10% in the 60+ age group, and mite-specific IgE showed a similar decline with age from 27% in the younger group to less than 10% in the older patients. In another study, Kerkhof et al stratified subjects into two age groups, old (45-70 years old) and young (20-44 years old), and noted a decreased prevalence (25% versus 40%) of positive RAST results to one or more allergens in the older cohort.[40]

Total IgE and Aging

While allergen specific IgE (RAST) and SPT are tools to assess allergic sensitization to specific allergens, total serum IgE value is a non-specific surrogate marker of the atopic state and has often been included in the routine evaluation of allergic asthma, severe atopic dermatitis, and allergic rhinitis. Many of the studies discussed above as well as numerous other studies examined the relationship between total serum IgE and the aging process.

IgE production is critically dependent on IL-4 as well as interactions between T- and B-cells. A study by Al-rayes et al suggest an age-dependent T-cell defect that results in reduced IL-4 and subsequent decline in IgE levels.[41] Along with allergen specific IgE, the studies discussed above by Stoy et al, Barbee et al, Wuthrich et al, and Sapigni et al also found lower total serum IgE levels in older patients compared to younger patients.[31,35-37]

Interestingly, there are some studies that have identified some exceptions to the general observation of declining IgE levels with age. Omenaas et al demonstrated a decreasing trend in total IgE with age in women compared to men (geometric mean 17.0 to 10.0 kU/I in women versus 15.5 to 20.9 kU/I in men).[38] Additionally, they noted that the highest levels of total IgE was observed in elderly men with a history of smoking. In a study by Kerkhof et al, the discriminating ability of total IgE to rule out clinical allergic sensitization was superior in younger subjects (age 20-44) than older ones (age 45-70) and comparable in males and females.[42] In other words, the negative predictive value of total serum IgE to exclude atopy was noted to be poor in the older population. Yet another study by Wittig et al performed on healthy and atopic individuals evaluated total serum IgE levels and noted a declining trend in asthmatic individuals but not in healthy subjects.[43] Overall, these data coupled with our knowledge of age-related changes in IgE production and regulation favor a declining trend of total serum IgE with age in normal and atopic individuals. However, care must be exercised when using total serum IgE as a measure of the atopic state given that it can be impacted by many confounding factors including sex, smoking status, concurrent infections (particularly parasitic) and environmental exposures.

A significant limitation of many studies examining age-effects on atopy is the cross-sectional design these studies. In contrast to the above studies, researchers in the UK noted an increase in atopy (as measured by RAST) in males over the last 35 years when comparing age-matched cohorts suggesting that more recent birth cohorts are more likely to be atopic. [44] Thus, it is possible that older cohorts were non-atopic to begin with and cross-sectional studies do not actually reflect a decline in atopy as a function of age. Similar findings and conclusions were drawn from a study in Denmark using repeated cross-sectional analyses.

[45] Additionally, the methods of evaluation and allergen extracts used (non-standardized in some cases) in the evaluation of these studies differ significantly amongst each other making it difficult to compare results. A number of studies are also inadequately powered to draw any meaningful conclusions. Despite these limitations, these studies do reiterate a consensus theme that allergen specific IgE values tends to decline with age, although individual allergens can display varying patterns of change with age.

Clinical Implications of Atopy on Aging

The existing data, despite its limitations, supports a decline in atopy with aging. If this decline does indeed occur, then it follows that the prevalence of allergic disease and associated morbidity and mortality should decline as well. However, it is not clear that this does occur. Rather, the prevalence, morbidity and mortality persist in some allergic diseases in older adults, specifically asthma.

Allergic Rhinitis in Older Adults

While allergic rhinitis has an estimated prevalence of 10-30% in adults, it has a mere 0.3% reported prevalence in those above age 65. A study of 107 allergic rhinitis patients by Simola et al who were allergy tested previously were re-evaluated after 23 years of follow-up to assess if a relationship between skin test reactivity and symptom severity exists.[46] While they noted a milder pattern of rhinitis symptoms along with decreased allergic skin reactivity with age, they concluded that these changes occur independently of each other. In addition, Hanneuse et al reported a declining trend with age in total serum IgE, circulating eosinophils, mean positive number of RAST as well as mean positive value of RAST to individual allergens that is more pronounced in atopic females than males.[47] Clinically, however, they noted a disconnect with a decreased corticosteroid requirement in younger atopic patients than older patients despite an increased prevalence in markers of atopy in the younger cohort. Raheison and colleagues found a strong relationship between percent positive RAST scores (40-42% in Asthma and/or allergic rhinitis versus 7% in healthy) and clinical symptoms of allergic rhinitis and asthma in elderly patients.[48] Similar results were shown in another large study on patients with rhinitis or asthma in which a significant decline in allergen reactivity was noted with age.[49] In summary, these studies do show that the clinical prevalence of allergic rhinitis also follows suit with the decline in atopic measures. This clinical picture may be a reflection of the changes of immunosenescence including impaired production of naïve T- and B-cells, impaired degranulation of basophils/eosinophils, decreased IgE production, and lower affinity antibody responses to allergens.

Atopy in Asthma in Older Adults

Despite the observation that allergic disease has decreased prevalence in the elderly, the severity of allergic disease remains a significant concern due to the fact that multiple organ systems suffer a functional decline similar to the immune system such that the ability to compensate during a period of stress is compromised. Decreased cardiac reserve, declining FEV1, poor vascular and smooth muscle tone are a few examples of age-related changes that may affect this compensatory response. Multiple studies have demonstrated that an atopic history appears to be the strongest predictor for asthma and its severity including in the elderly.[50,51] The changes of immunosenescence are thought to render older adults more susceptible to respiratory infections, and likely contributes to increased utilization of health care resources.[52] One other factor contributing to increased morbidity of allergic disease in the elderly is their poor perception of allergic disease symptoms.[53,54] These observations validate the concern for allergic disease monitoring in the elderly and the need for an appropriate atopic evaluation.

There are likely distinct phenotypes to include an early-onset allergic asthma and a late-onset asthma that is typically non-allergic. In the NIH sponsored severe asthma research program (SARP), Moore et al have been able to segregate asthmatics into various phenotypic clusters based on their time of onset for asthma, baseline lung function, and atopic state.[55] As we have already stated, atopy is the single strongest predictor of asthma and its severity in all age groups including the elderly.

One of the largest multi-center evaluation of asthma in the elderly was conducted as part of the TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) study.[56] The authors noted lower mean total serum IgE levels, lower prevalence of comorbid allergic rhinitis or atopic dermatitis in older patients compared to younger ones, but had worse lung function as measured by pre-bronchodilator and post-bronchodilator forced expiratory volume in 1 sec (FEV1). An interesting, yet discordant, observation was that older cohort had lower health care utilization (HCU) compared to the younger cohort despite having worse lung function perhaps reflecting higher use of inhaled corticosteroids and aggressive management. The Veterans Administration (VA) Normative Aging study has been an important source of clinical and biological information to help dissect the relationships between atopy and asthma. One analysis evaluated three phenotypic markers of atopy (SPT, total IgE, and eosinophilia) against respiratory syndromes (asthma, hay fever, cough/phlegm production). Total serum IgE was noted to be increased against all respiratory syndromes with the strongest association noted for asthma while SPT positivity was most strongly associated with hay fever and asthma. Based on this analysis, the authors recommend, at a minimum, an assessment of total IgE and skin prick testing in patients with asthma and allergic rhinitis.[10] Another subset analysis found that new-onset wheezing in older adult male population was significantly associated with allergic sensitization to dust mite.[11] Two nested case-control studies of the Normative Aging Study by Litonjua et al revealed a strong relationship between allergic sensitization to cat allergen and both asthma and new-onset airway hyperresponsiveness.[57] This relationship was not noted for dust mites or ragweed allergens. Scichilone and colleagues also make a similar recommendation for an assessment of atopy in elderly subjects with airway hyperresponsiveness as it is considered an independent predictor for airway hyperresponsiveness.[51] Similarly, a study by Kerkhof et al on 1927 patients with a mean age of 44 demonstrated that total IgE had a significant dose-response relationship with AHR in older subjects independent of allergen sensitization and that the association between allergic sensitization and AHR predicates upon the nature of the allergen and the level of specific IgE.[42]

Interestingly, contrary to results from previous studies, a study by Crawford et al on male asthma patients found that SPT positivity and total IgE levels did not decline with age implying that IgE-dependent mechanisms of inflammation continue to play a role in elderly asthma patients.[58] Huss et al also reported a high prevalence of SPT positivity, particularly to indoor allergens, among moderate to severe persistent elderly asthmatics and associated it with significantly lower quality of life (QOL) scores.[59] In reviewing all these studies, there is a striking observation that atopy has a strong association with asthma of varying severity regardless of age. However, we are lacking in studies that correlate the degree of atopy to asthma severity or the relative contribution of atopy to asthma exacerbations.

In a report by Maykut et al, a pooled analysis of asthma patients treated with omalizumab (anti-IgE) was performed and demonstrated that older (above 50 years old) asthma patients also benefited from its use with respect to decreases in exacerbations, β -agonist use, and asthma symptoms.[60] Since the mechanism of omalizumab is directed at the atopic axis, this study provides evidence that IgE and atopy have direct clinical relevance to asthma in

older adults. Therefore, this study provides support for an assessment of allergic sensitization, either by SPT or RAST, in older asthma patients.

Conclusion

Aging is complex process that involves changes to all organ systems in our body including the immune compartment. These immune changes, also known as immunosenescence, are thought to play a role in the prevalence and severity of allergic diseases in the elderly. Based on the data from various studies, there appears to be a consistent observation that atopy as measured by SPT, RAST or total IgE declines with age. Nonetheless, the association between allergic sensitization and allergic diseases, particularly asthma and allergic rhinitis, remains robust in the elderly population. Consequently, an appropriate evaluation of atopy is warranted and indicated in older asthma and rhinitis patients in order to provide optimal care for the individual and minimize any resultant morbidity and mortality.

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