Serum allergen-specific IgE, allergic rhinitis severity, and age*

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Abstract

Background: Allergic rhinitis (AR) is characterized by an IgE-mediated reaction. Aging usually induces a progressive decline of immune system function. There is common belief that both allergic symptoms severity and serum IgE production decline during aging.

Objective: This study aimed to evaluate the possible impact of age on: i) serum allergen-specific IgE levels in a large sample of subjects, and ii) AR symptom severity in a group of mono-allergic patients.

Methods: Serum allergen-specific IgE to birch, Bet v 1, *Parietaria*, and *Dermatophagoides pteronyssinus* were measured by immunofluorometric assay (IFMA) in a sample of 8098 subjects. AR symptom severity was assessed by visual analogue scale (VAS) in a sub-group of 531 mono-allergic patients.

Results: The analysis of variance showed that IgE to Bet v 1, birch, and *Dermatophagoides pteronyssinus* significantly decreased considering the age, whereas IgE to *Parietaria* did not significantly decline in respect of the age. Considering the global sample of mono-allergic patients, elderly subjects (> 65 years old) tended to have lower IgE levels, but had significantly lower VAS rating, and significantly less sensitizations than adult subjects (18-65 years old). In both adult and elderly patients VAS strongly correlated with IgE values.

Conclusions: Allergen-specific IgE levels tend to reduce with aging, but with differences between types of allergy. The IgE decrease is usually associated with reduced AR symptom severity. Elderly AR patients seem to have a different phenotype/endotype in comparison with adult AR ones, characterized by milder symptoms, lower IgE production, and less sensitizations. However, a close positive relationship between IgE values and VAS scores is shared by both adult and elderly AR patients, confirming the close link between allergy and symptoms that persists also in the elderly.

Key words: allergen-specific IgE, age, allergic rhinitis, serum, symptom severity

Introduction

Allergic rhinitis (AR) is a very common immune-mediated disease as far as the prevalence is up to 40% of the general population, mainly in childhood and young adulthood. However, AR is still a relevant issue also during old age for some aspects, including the remarkable number of elderly people and the continuously increasing quote of over 65 over time, the relevant consume of health care resources by old patients, and the chronic impact of environmental factors on airways. In this regard, it has been appraised that the prevalence of allergic disorders in the elderly is about 10%, but it appears to be rising [(1)].

A progressive decline of almost all the functions of organs and systems characterizes aging [(2)]. In particular, aging significantly affects the immune system with relevant changes, defined as "immune-senescence" [(3-5)]. The hematopoietic potential maintains preserved function under basal condition, but the

stem cell renewal gradually declines during stress with aging. Secondary lymphoid tissues show age-dependent architectural modifications. Generally, a reduced antibody production, mainly against new encountered antigens and/or as response to vaccinations, is present in elderly subjects as well as an impaired dendritic cell activity. In addition, change in organs structure and function influences the natural history of allergy, complicated by comorbidity, poly-therapy, and adverse reaction to drugs. In particular, one of the most relevant change concerns the absolute age-depending reduction of total T cells, including both CD4 and CD8 subpopulations, as well as of naïve T cells and memory T cells [6]. In addition, a shift in cytokine pattern from the physiological T helper 1 polarization to T helper 2 has been reported [7]. It was also observed an increase of circulating eosinophils associated with increased interleukin 6 levels in older women [8]. This fact is interesting as a typical marker of allergic reaction, such as eosinophil, correlates with a biomarker (IL-6) of age-related systemic inflammation: in fact, in elderly subjects a state of chronic inflammation may occur, typically defined as "inflamm-aging"[9]. Generally speaking, there is evidence for a decline in some function of the immune response, but the clinical relevance is not still completely clear.

AR is defined by a nasal inflammation consequent to the IgE binding with the inhaled causal allergen. Thus, IgE may be considered as the hallmark of allergic reaction. IgE production may be easily detected by skin prick test (SPT) and serum allergen-specific IgE measurement. SPT is the most used tool for assessing allergy in all age groups. However, the sensitivity of SPT, reflecting skin mast cell function, decreases in the elderly. Really, age-dependent cutaneous modifications, such as atrophy, reduction in mast cells and vasculature, and common use of drugs, including antihistamines, tricyclic antidepressants, anti-serotoninergic agents, may significantly affect SPT results. For this reasons, serum IgE assessment seems to be a more reliable way to investigate the impact of age on IgE production [10-12]. There is evidence, based on selected and unselected populations, that IgE production usually tends to decline with age. A Dutch general population study documented that serum IgE levels were lower in the oldest subpopulation, such as 45-70 years[13]. This result was confirmed in stratified population sample with age range between 8-73 years [14]. Another study, conducted on general population with age between 19-99 years, confirmed that the elderly subjects had the lowest IgE levels[15]. Moreover, studies on allergic patients reported consistent findings: the older patients usually have the lowest IgE levels [16-20]. However, these surveys were conducted on relatively limited samples of allergic patients, and seldom with narrow age ranges. In addition, the possible impact of aging on allergic symptom severity reduction was not adequately investigated. Therefore, the present study investigated the possible impact of age on: i) allergen-specific IgE production, such as the endotype, and ii) AR clinical severity, such as the phenotype.

Materials and methods

Patients

This retrospective study is based on two parts, considering two distinct selected populations of adult patients.

Endotype analysis

This part of the study analyzed the impact of age on sensitization pattern, including prevalence and IgE levels. The sample consisted of 8,098 subjects (48% females; mean age 41.1 years; age range: 18-102 years). All of them suffered from respiratory complaints suggestive for allergy. The considered period ranged from January 2007 to December 2014.

As the patients were sent by General Practitioners or specialists to the Laboratory of the IRCCS-A.O.U. San Martino of Genoa (Italy) for serologic assessment, a common panel of tested allergens was not shared for all patients. Nevertheless, the most common allergen-specific IgE assessed in our lab are: grasses, Parietaria, olive tree, birch, Dermatophagoides, cat, and dog. For this reason, we analyzed the findings of serum allergen-specific IgE to the 3 most relevant causal allergens in our area [21], such as *Dermatophagoides pteronyssinus* (6190 subjects), birch (3742 subjects) including its major allergen Bet v 1 (2281 subjects), and *Parietaria* (3112 subjects). *Dermatophagoides pteronyssinus* is the most common House Dust Mite causing allergy in our area. However, the data concerning SPT were missing for most patients for the above mentioned reasons.

Phenotype analysis

The second part of the study analyzed the impact of the age on AR symptom severity in a very selected group of AR patients, consecutively visited at the Allergy department. The sample included 530 subjects (53% females, mean age 44.9 years; age range 18-89 years). The inclusion criteria were: i) adult age, ii) AR diagnosis, and iii) mono-allergy to a specific allergen, such as allergy to *Dermatophagoides pteronyssinus*, or to birch, or to *Parietaria*. These mono-allergic patients were subdivided in 3 sub-groups according to the specific allergy: 190 were mono-allergic to *Dermatophagoides pteronyssinus* and hence defined as mite-allergy sub-group, 176 were mono-allergic to *Parietaria* defined as *Parietaria*-allergy sub-group, and 164 were mono-allergic to birch, birch-allergy sub-group.

AR was diagnosed according to validated criteria proposed by ARIA guidelines [22]. Mono-allergy is defined as the presence of an allergy to one allergen alone, even though other sensitizations may co-exist. In this regard, allergy is considered when symptom history is consistent with exposure to the sensitizing allergen.

We considered AR symptom severity measuring the patients'

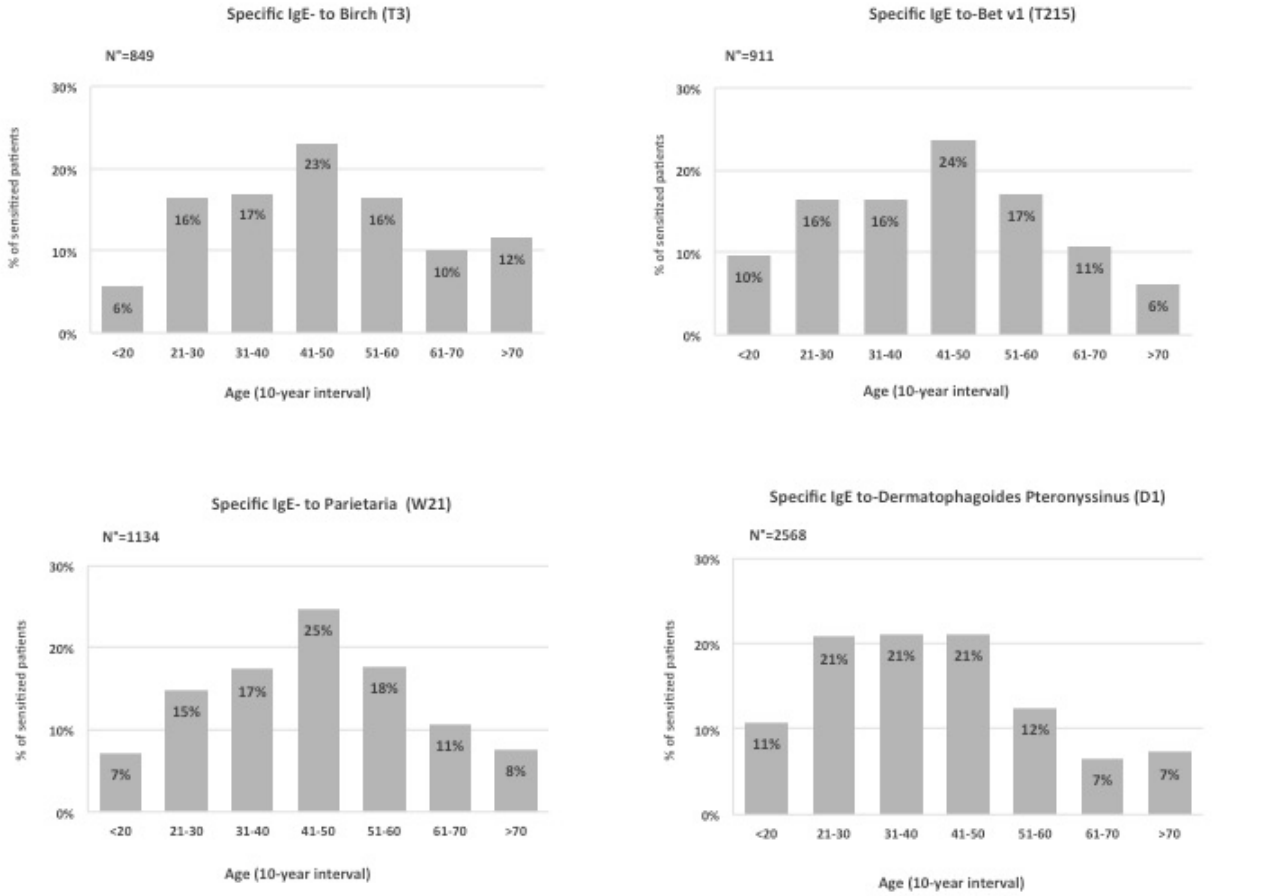

Figure 1. Percentages of sensitized patients considering age classes and evaluating separately birch, Bet v 1, *Parietaria*, and *Dermatophagoides pteronyssinus*.

perception by the visual analogue scale (VAS). The VAS scores were recorded in season for the pollen-allergic patients.
All patients gave the written informed consent and the Review Board of the IRCCS-AOU San Martino approved the procedure.

IgE assay

Serum levels of specific IgE were detected by the IFMA procedure (ImmunoCAP Thermo Fisher Scientific, Uppsala, Sweden) in peripheral blood samples from patients. Serum was collected into gel-separator tubes, centrifuged and stored at -20°C until analysis for: *Dermatophagoides pteronyssinus*, Bet v 1, birch, and *Parietaria*. Measurement of circulating specific IgE antibodies was performed according to manufacturer's instructions [23]. Specific Ig E concentrations were expressed in kUA/L according to the traceable calibration to the 2nd IRP WHO for Human IgE and 0.35 kUA/L has been considered as a cut-off [24].

Visual analogue scale (VAS)

The VAS consisted of one ruler asking for nasal symptom [25]. The VAS was a 10-cm horizontal line on which 0 implied no symptom, while 10 corresponded to the most severe symptoms. With a movable marker, the subject could mark any point on the 10-cm segment which best described his/her perception. No interval marker was visible on the line.

Statistical analysis

Distributions of allergen-specific IgE levels by gender and age were graphically explored and described using means and standard deviation. Age-specific trend of each allergenic biomarker in both genders was estimated through a general linear regression modeling (Kleinbaum). In order to point out nonlinear tendencies, age was categorized into seven 10-year groups and modeled as a set of indicator variables. The non-parametric Kruskal-Wallis rank test was performed to evaluated the analysis of variance between groups of allergens. Relationship between VAS values and age was calculated by Pearson test. T test of Student was used for comparing clinical and immunological characteristics between adult and elderly patients. Data were recorded and analyzed on the Microsoft EXCEL: Windows 7 enterprise platform (Microsoft Co, Richmond, WA, USA) and

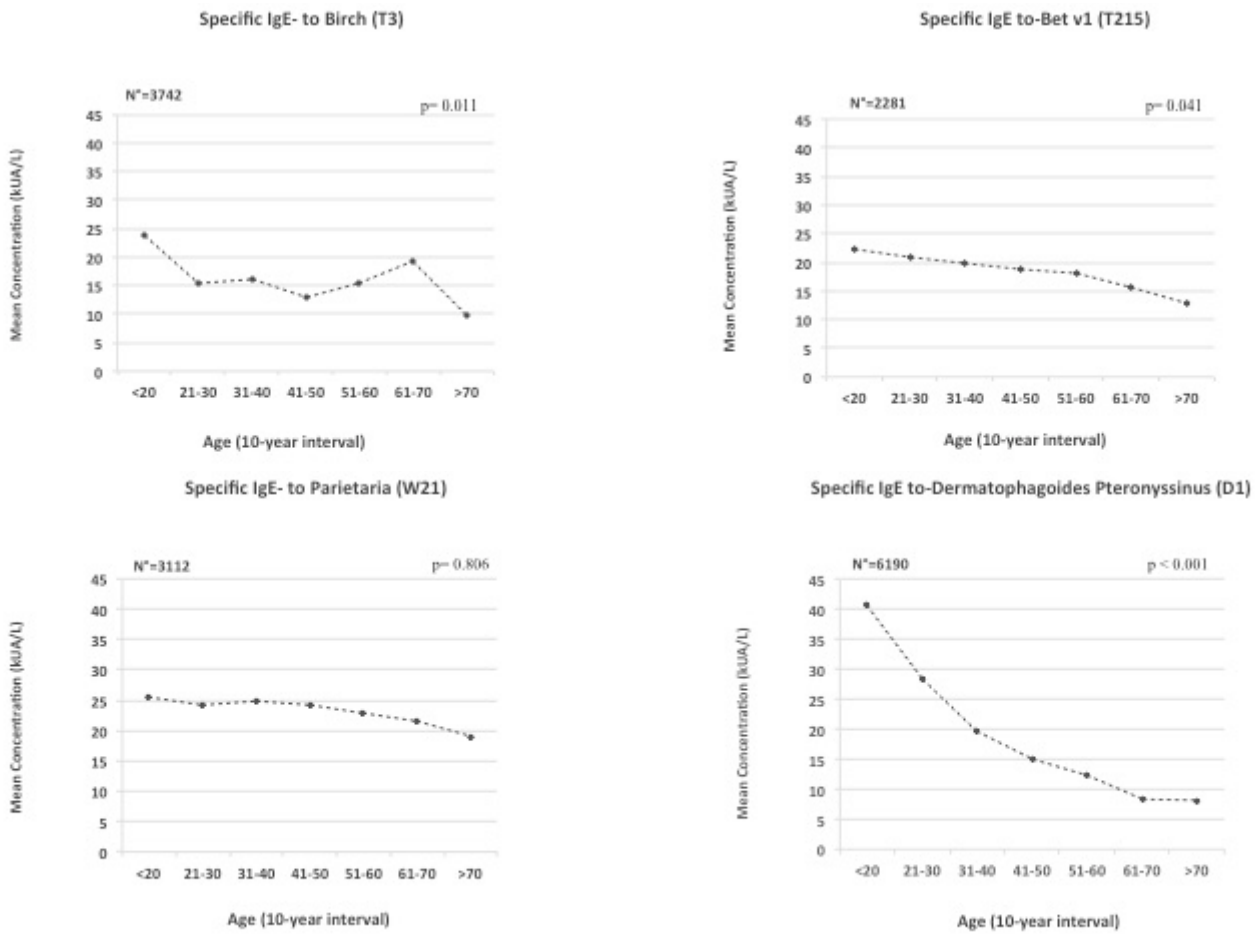

Figure 2. Serum specific IgE levels among the groups of patients, evaluating separately birch, Bet v 1, *Parietaria*, and *Dermatophagoides pteronyssinus*. Serum concentrations were expressed as mean values.

statistical calculations were performed by means of Med Calc® statistical package ver 12.4.0. (Med Calc® software Corporation, Mariakerke Ostend, Belgium).

Results

Endotype analysis

Figure 1 reports the frequency of distribution (expressed as percentage) of serum allergen-specific IgE positivity (such as > 0.35 kUA/L), defined as sensitization, in relation to the age of all patients for each specific tested allergen. Globally, 23% of subjects tested for birch (T3) were sensitized, 40% for Bet v 1 (T215), 36% for *Parietaria* (W21), and 42% for *Dermatophagoides pteronyssinus* (D1). The analysis of the impact of age on sensitization distribution showed that patients sensitized to pollen allergens had a peak in the 41-50-year interval, whereas mite-sensitized patients had a plateau between 21 and 50 years. Before all peaks the sensitization percentages were increasing, whereas after the peaks the percentages were always decreasing.

Figure 2 shows the distributions of serum IgE levels, specific for the single allergens, in relation to the age. In particular, serum IgE levels to birch, Bet v 1, and *Dermatophagoides pteronyssinus* showed statistically significant reduction (p=0.041; p=0.011; p<0.001 respectively), whereas IgE levels to *Parietaria* did not significantly decline in respect of the age (p=0.81). It is of note that the IgE decreasing trend is very clear-cut only for mites. On the contrary, the decreasing slope for birch and Bet v 1 is rather slight.

Finally, no allergen-specific IgE gave rise to biologically discernible and statistically detectable differences by gender (data not shown).

Phenotype analysis

The group of mono-allergic patients was subdivided in two subgroups according to the age: adult subjects (18-65 years) and elderly subjects (>65 years). Then, the patients were evaluated globally and after subdivision in 3 sub-groups according to the causal allergen. Table 1 shows the comparison between adult and elderly mono-allergic patients considering gender, serum IgE levels, perception of allergic symptom severity assessed by

Table 1. Clinical and immunological characteristics of AR patients considering the age: adult (< 65 years) and elderly (> 65 years) patients.

All Patients		TOTAL (N=531)	AGE ≤ 65 (N=462)	AGE> 65 (N=69)	p-value
Gender	Males (%)	49	48	52	
IgE [kUA/L]	(mean)	18.4 ± 7.3	19.6 ± 7.2	13.6 ± 6.0	0.07
VAS	(mean)	7.3 ± 1.7	7.5 ± 1.6	5.5 ± 1.5	<0.0001
N. SENSIT.	(mean)	1.4 ± 0.4	1.6 ± 0.3	1.4 ± 0.2	<0.05
Mite Allergy		**TOTAL (N=174)**	**AGE ≤ 65 (N=150)**	**AGE> 65 (N=24)**	**p-value**
Gender	Males (%)	51	51	50	
IgE [kUA/L]	(mean)	18.2 ± 10.1	20.2 ± 9.8	7.8 ± 0.6	<0.0001
VAS	(mean)	6.9 ± 1.8	7.3 ± 1.5	4.3 ± 0.9	<0.0001
N. SENSIT.	(mean)	1.5 ± 0.5	1.7 ± 0.6	1.3 ± 0.3	<0.05
Parietaria Allergy		**TOTAL (N=183)**	**AGE ≤ 65 (N=161)**	**AGE> 65 (N=22)**	**p-value**
Gender	Males (%)	47	46	55	
IgE [kUA/L]	(mean)	23.2 ± 2.2	24.3 ± 4.1	20.3 ± 1.8	0.1
VAS	(mean)	7.3 ± 1.6	7.5 ± 1.6	6.0 ± 1.3	0.0001
N. SENSIT.	(mean)	1.6 ± 0.5	1.7 ± 0.4	1.6 ± 0.7	0.6
Birch Allergy		**TOTAL (N=174)**	**AGE ≤ 65 (N=151)**	**AGE> 65 (N=23)**	**p-value**
Gender	Males (%)	48	48	48	
IgE [kUA/L]	(mean)	15.9 ± 4.2	16.5 ± 4.1	13.0 ± 4.5	0.04
VAS	(mean)	7.6 ± 1.6	7.8 ± 1.5	6.3 ± 1.52	<0.0001
N. SENSIT.	(mean)	1.9 ± 0.8	1.8 ± 0.8	1.7 ± 0.6	0.08

VAS, and number of sensitizations.

Considering the global sample of mono-allergic patients, elderly subjects (69) tended to have lower IgE levels (p= 0.07), but had significantly lower VAS rating (p<0.0001), and significantly lower number of sensitizations (p<0.05). About mono-allergic patients to mites (i.e. *Dermatophagoides*), adult patients had significantly higher IgE levels (p<0.0001), significantly higher VAS (p<0.0001), and significantly more sensitizations (p<0.05) than elderly patients. About *Parietaria*-allergy, elderly patients had only significantly lower VAS rating than adult ones (p<0.0001). About birch-allergy, elderly patients had significantly lower IgE levels (p=0.04), and significantly lower VAS rating (p<0.0001) than adult patients.

Correlation between phenotype and endotype

Figure 3 reports the relationships between VAS scores for AR symptom severity and age of patients. All patients showed a significant (p<0.0001) decrease of symptom severity associated with aging. However, the inverse relationship was very strong (r= -0.82) for mite-allergic patients, but moderate for birch-allergic patients and *Parietaria*-allergic ones (r= -0.48 and -0.47, respectively).

Subdividing all mono-allergic patients in adult sub-group and elderly sub-group, VAS values were compared with allergen-specific IgE levels: in adult patients VAS strongly and positively correlated with IgE (r=0.71) as well as in elderly subjects (r=0.62).

Discussion

AR is a very common and vexing condition also during the aging [12,26]. However, there is common belief that AR prevalence and allergic symptoms severity trend to diminish with aging.

Serum IgE is commonly considered the typical biomarker for the allergic reaction, as allergic disorders are paradigmatically characterized by an IgE-mediated inflammation. So IgE measuring is a popular way to assess allergy.

The present study aimed to investigate the impact of age on allergen-specific serum IgE production and successively the possible impact of aging on AR symptom severity.

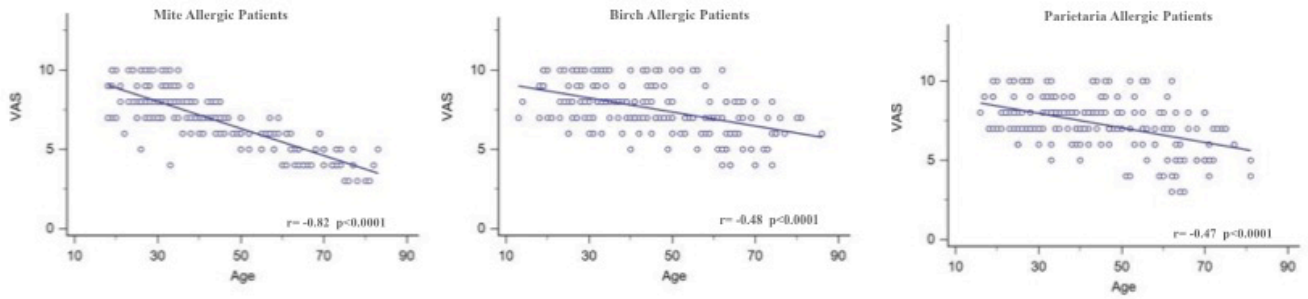

Figure 3. Relationships between VAS of respiratory symptoms and age in patients mono-allergic to mites, birch, and *Parietaria*.

The first part of the study was conducted on a large sample of selected subjects, with suspected AR diagnosis, who referred to a serologic assessment. Thus, this step was oriented to the endotype analysis as it considered only sensitization pattern, such as serum IgE positivity, evaluated in terms of prevalence and levels. The percentage of sensitized subjects was 23% for birch, 40% for Bet v 1, 36% for *Parietaria*, and 42% for *Dermatophagoides pteronyssinus*. These findings confirm that these allergens are very common in our geographic area. The higher rate for Bet v 1 sensitization in comparison with birch sensitization might depend on the characteristics of requiring doctors: in fact, allergists prefer to assess Bet v 1 so the sample may be more selected.

Age had an impact on allergen-specific IgE production in a way different for every allergen, both considering the sensitization prevalence and the serum level distributions. *Dermatophagoides* sensitization concerned essentially younger subjects, whereas sensitization to pollen allergens typically showed a peak in the middle age. These conflicting findings could depend on the duration of allergen exposure: perennial for mites and seasonal for pollens. In other words, a continuous allergen pressure (e.g. induced by mites) may induce a more intense and precocious sensitization than a periodic one (e.g. pollens). In addition, pollens could be able to stimulate the immune system to produce IgE with a stronger ability than mites. It seems that pollens might have a more intense antigenic activity than mites as suggested by some studies [27,28]. Globally, these findings highlight the decline trend of IgE production in the elderly.

The clinical relevance of these findings was supported by the second part of the present study, concerning the impact of age on AR symptom severity, such as oriented to consider the phenotype. The inverse relationship between symptom severity perception and age was stronger in mite-allergic patients than in pollinosic patients. Pollen-allergic patients trend to complain allergic symptoms also in elderly, even though with lesser intensity. Therefore, the IgE level reduction associated with aging may have a clinical impact on symptom severity.

In addition, we compared clinical (symptom severity, such as the phenotype) and immunological (sensitization pattern, such as the endotype) characteristics between adult and elderly patients. Actually, elderly patients seem to have a different phenotype/endotype in comparison with adult subjects. Elderly AR patients have milder symptoms, lower IgE levels, and less sensitizations than adult patients. On the contrary, there was a similarity between adults and elderly concerning the close relationship between IgE values and symptom severity: higher IgE levels correspond to higher VAS values.

Another interesting finding concerns the prevalence of AR in elderly patients: about 13% in our selected population of outpatients. This outcome underlines the relevance of AR also in older subjects.

The findings of the present study are substantially consistent with previous studies. A series of studies investigated the impact of age on IgE production, whereas other studies analyzed AR prevalence and symptom severity considering the age. About allergen-specific IgE and aging, a first study, conducted by Stoy and colleagues, reported a statistically significant decrease with age for Alternaria, house dust mite, and Timothy grass, but not for monilia, Aspergillus, and ragweed, with regard to SPT and RAST results [29]. A Swiss study, enrolling a large general population sample, reported that allergen-specific IgE and allergic diseases declined by 23% and 21% with every 10-year increase in age [30]. Omenaas and colleagues demonstrated that there was a significant decline in the prevalence of allergen-specific IgE to some common allergens over time [31]. Consistently, Nakazawa confirmed a decline of allergen-specific IgE to Japanese cedar pollen with aging [15]. Also Kerkhof showed a decreased prevalence of positive serum IgE assay in older subjects [13]. Concerning the AR prevalence, Yonekura and colleagues evaluated a group of 703 Japanese subjects followed over 10 years [32]. These authors found that the prevalence of AR to cedar pollen decreased with age during the study, even though the prevalence of AR was higher in 2005 than in 1995 because the levels of pollen exposure increased in the same period. Blomme and colleagues performed a study on a large general unselected population sample (age range 3-86 years): both positive SPT and AR prevalence significantly and progressively decreased with aging [33].

However, a relevant variable in these studies concerns the geographical differences about allergen exposure. In this regard, some Italian studies evaluated this issue. Ventura and colleagues evaluated 54 elderly patients and 89 young adults suffering from AR [34]. They reported that there was not difference concerning total IgE levels between groups as well as cytological findings, but the epithelial-globet cells ratio was decreased in elderly patients; the quality of life was also more impaired in older subjects. Di Lorenzo and colleagues evaluated a group of 108 AR patients and followed them for a 15-year follow-up: rhinitis symptoms became milder over time as well as serum-specific IgE diminished at follow-up [35]. Cazzoletti reported a significant decline in self-reported AR prevalence from 26.6% in younger subjects to 15.6% in the elderly, without gender difference [36]. Very recently, Lombardi noted that AR comorbidity was 47.6% in elderly asthmatics, AR preceded asthma onset, and mite sensitization was associated with uncontrolled asthma; thus the authors concluded that AR is a relevant factor in asthma also during the elderly [37].

All these studies agree about the evidence that serum IgE levels and AR symptom severity generally decrease with aging, even though AR may still persist during senescence. Consequently, the management of elderly AR patients should be tailored considering the specific characteristics of old age [38].

This study had some limitations: it was retrospectively conducted on selected patient population samples, such as without AR diagnosis in the first part and considering mono-allergic patients alone in the second part, it was cross-sectional, and it did not evaluate the single AR symptoms (itching, sneezing, rhinorrhea, and congestion). In addition, this study did not consider possible confounding factors, such as smoking status, parasite infestation, environmental exposures, seasonal variations, and skin prick test findings. Therefore, there is the need to conduct cohort studies and long-term follow-up trials to confirm these preliminary findings. Another shortcoming of the present study was the lack of information regarding non-allergic subjects with rhinitis, as it could be important to report how the prevalence of non-allergic rhinitis varied with age. Thus, a further study should address also this issue.

Conclusion

In conclusion, allergen-specific IgE levels tend to reduce with aging, but with differences between types of allergy. The IgE decrease is usually associated with reduced AR symptom severity. Elderly AR patients seem to have a different phenotype/endotype in comparison with adult AR ones, characterized by milder symptoms, lower IgE production, and less sensitizations. However, a close positive relationship between IgE values and VAS scores is shared both by adult and elderly AR patients, confirming the close link between allergy and symptoms that persists also in the elderly.

Authorship contribution

GC designed the study and wrote the paper, PC and FF collected sera and performed Ian analysis, MB and VF analyzed data, MM discussed the paper.

Conflict of interest

No conflicts of interest to declare.

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