

Original article

IgE level and Phadiatop[®] in an elderly population from the PAQUID cohort: relationship to respiratory symptoms and smoking

Background: In the last decades in industrialized countries, the increase of life expectancy has resulted in an increase in the population of the elderly. However, little is known about the prevalence of allergies in the elderly population. The aim of the study was to investigate the specific relationship of serum IgE and Phadiatop, with asthma, rhinitis, and smoking in a sample of an elderly population.

Methods: Subjects from the Paquid cohort living in Gironde Department (age 65 years and over) in France were followed up since 1988 (PAQUID cohort).

Results: Among the randomized sample of 352 subjects, there were 158 men (45%) and 194 women (55%). The lowest levels of IgE were in subjects with chronic sputum; and in normal subjects (47.1 ± 56.4 vs 56.2 ± 73.9 , NS). Multiple linear regression was performed with $\log_{10}$ IgE values as a dependent variable and age, Phadiatop test, smoking, and respiratory symptoms independently in men and in women. In men, a significant relationship was observed between IgE values and Phadiatop test ($P < 0.001$), asthma history ($P = 0.002$), and smoking ($P = 0.019$).

Conclusions: Respiratory allergy is present in persons >65 years of age. There is an association between smoking and IgE level independent of allergic reactivity to common allergens in the elderly.

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Key words: allergies, asthma, cohort, elderly, rhinitis,
smoking.

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Accepted for publication 17 December 2003

The identification of IgE in the mid-1960s has considerably increased the understanding of allergy in respiratory diseases. Epidemiological studies have linked high serum levels of IgE with asthma and rhinitis both in the young and adults (1). In addition, IgE level has been related to smoking (2, 3). Such a relation remains unexplained, although the potential role of smoking in the pathogenesis of immunological disease has been raised (4). Nevertheless, in the Normative Aging Study no association was found between IgE and the decline of lung function according to smoking (5).

Data from the European Community Respiratory Health Survey (ECRHS) suggest variations of IgE in the general population (6). Similarly worldwide variations in the prevalence of asthma and rhinitis have been described in the International Study of Asthma and Allergies in Childhood (ISAAC).

In the last decades in industrialized countries, the increase of life expectancy has resulted in an increase in

the population of the elderly. It is common knowledge that elderly people fail to develop protective immunity after immunization with influenza and pneumococcal vaccine (7). In this way, some studies have shown a significant age-related decline of IgE apparent for both gender, with levels in females being significantly lower than in males (8–10). In addition, bronchial asthma has been underestimated (1) and hence undertreated in elderly cohorts (11); 30% of the asthmatic adults (12) are aged over 60 years in Japan and 12.4% are aged 65–74 years in USA. It was recently found out that late-onset asthma may represent the extreme end of a spectrum of age-associated b-adrenergic dysfunction (12) and attention has been focussed on the evaluation of allergic status in the elderly (13).

Personnes âgées quid (PAQUID) is a cohort of subjects aged 65 years and over living at home in south-west France. The aim was to study the factors and consequences of ageing (14); 6% had asthma, often associated

with chronic bronchitis or dyspnoea (15, 16). Compared with others, asthmatics had a higher risk of disability in daily life (17) and mortality. Late-onset asthma was frequent. Risk of mortality remained significantly higher for smokers and ex-smokers.

The aim of the study was to investigate the specific relationship of serum IgE and Phadiatop, with asthma, rhinitis, and smoking in this cohort.

Methods

Population sample

Subjects from the Paquid cohort living in Gironde Department (age 65 years and over) were followed up every year since 1988 (PAQUID cohort). They had been randomly selected from electoral lists after stratification on age (65–74, 75–84, and 85 years and more), gender and urban unit basis (less than 2000, 2000–9999, 10 000–49 999, 50 000 inhabitants and more). The methodology and the main results of PAQUID have been previously published elsewhere (14). Of these 2792 elderly subjects, 636 (23%) agreed to undergo venous blood withdrawal for Paquid serotec. For financial reasons, a random sample of 352 subjects were only considered for blood withdrawal.

Data collection

Questionnaire. Elderly subjects were interviewed at home by trained psychologists. Appointments were made by telephone or letter and then a 1-h home interview was conducted. If the subject was unable to answer, the help of a proxy was sought. Questionnaire variables included sociodemographic items (age, gender, past occupation, educational level), assessment of functional disability and health status (including respiratory variables), a set of psychometric tests, and current medication. Principal lifetime occupation was classified according to the French 'Institut National de la Statistique et des Etudes Economiques' (INSEE) classification. Assessment of functional disability, health status and psychometric tests has been published elsewhere and will not be considered in the present paper.

The respiratory part of the PAQUID programme took place since the third year of the follow-up, because of the absence of respiratory questions in the first survey except dyspnoea and smoking habits. Identification of asthma, was based on the subjects' responses to the following two direct questions: 'Have you ever had asthma?', 'Did you have at least one asthma attack in the last 12 months?' Subjects were afterwards grouped as follows: 'current asthma' defined as at least one asthma attack within the past 12 months, 'asthma history' defined as suffering from asthma previously.

No data about use of specific regimen, or follow-up by a specialist physician were recorded. Others symptoms were collected during the 5-year follow-up by questionnaire, 'nasal allergy', 'morning cough' and 'chronic sputum'. According to Fletcher's recommendation, we defined chronic bronchitis as phlegm for most days for at least 3 months/year for the two previous years and dyspnoea was defined according to the Fletcher's scale. 'Current smokers' were those who smoked regularly at the period of the administration of the questionnaire. 'Former smokers' were defined as those who formerly smoked but no longer did so. 'Never-smokers' is self-explanatory. Quantification of tobacco in pack-years (PY) was taken into account for current and former smokers, considering the duration of smoking and number of cigarettes smoked every day.

Total serum IgE and Phadiatop. Blood samples were collected at home by a nurse from volunteers. Total serum IgE determination (kU/l) was performed by a direct paper radioimmunosorbent test (Prist; Pharmacia Diagnostics AB, Uppsala, Sweden). Each test was performed in duplicate and the average of the two values of each sample was recorded. When the coefficient of variation between the two measurements was > 10%, the test was repeated. This method has a detection limit of approximately 0.1 kU/l.

For ethical reasons it was not possible to assess allergic reactivity to common allergens by skin tests. So the concentration of serum IgE antibodies against 10 airborne allergens present in a solid phase was assayed with the Phadiatop test with the capsulated hydrophilic carrier method (Phadiatop/Cap system FEIA; Pharmacia Diagnostics AB). The results were expressed as positive (allergic) or negative (non-allergic).

Statistical analysis

First we described the sample: the socio-demographic characteristics, smoking, respiratory and biological variables. An univariate analysis was then performed using chi-squared, Wilcoxon and Mann-Whitney tests. As IgE distribution was non-normal, statistical analyses were carried out using $\log_{10}$ IgE values. Finally, two multivariate analyses were performed: a multiple linear regression with IgE ($\log_{10}$) as dependant variable and a logistic regression with a Phadiatop test (positive or negative) as a dependent variable. Statistical analysis was performed using the STATA 6.0 software (STATA Corp., College Station, TX).

Results

Descriptive analysis

No difference was observed between the 636 (23%) subjects who consented to venous blood withdrawal for Paquid serotec and others with regard to age (75 ± 6.5 vs 76.5 ± 7 years), gender (42.6% of men vs 39.5%), smoking (61% of never smokers vs 64%), asthma (5% vs 7%; $P = 0.12$), rhinitis (15.7% vs 14.6%; $P = 0.58$) and chronic bronchitis (14.1% vs 11.5%; $P = 0.13$).

Among the 352 random subjects involved, there were 158 men (45%; mean age 74 ± 5 years) and 194 women (55%; mean age 75 ± 7 years). Table 1 presents the general characteristics of men and women. There were no differences according to the gender for educational level but the difference was significant ($P < 0.001$) for matrimonial status (higher proportion of widowed women). Smoking was significantly different in both genders ($P < 0.001$) with a higher proportion of smokers and ex-smokers among men (15.9 and 53.5%) than in women (6.7 and 9.4%). In smokers cigarette consumption was also significantly higher ($P = 0.014$) in men (29.4 PY) than in women (14.7 PY). Dyspnoea (level 2 and more) was significantly higher in women: 26.8% vs 15.2% in men ($P = 0.011$). Chronic sputum and morning cough were significantly higher in men [20.3% vs 10.3% ($P = 0.016$) and 17.8% vs 8.2% ($P = 0.018$), respectively].

Total IgE (mean $\pm$ SD) was 85.2 ± 204.6 kUI/l in the population. Total IgE levels (mean $\pm$ SD) were higher in

Table 1. Description of the sample

	Men (n = 158)	Women (n = 194)	P-value
Age (mean $\pm$ SD)	74 $\pm$ 5	75 $\pm$ 7	NS
Matrimonial status			<0.001
Married	125 (84.5)	68 (36.6)	
Widowed	14 (9.5)	97 (52.1)	
Single	1 (0.7)	7 (3.8)	
Others	8 (5.3)	14 (7.5)	
Education level			NS
No education	33 (20.9)	54 (27.8)	
Primary school	79 (50.0)	86 (44.4)	
Secondary school	32 (20.2)	45 (23.2)	
Superior school	14 (8.9)	9 (4.6)	
Smoking			<0.001
Current smokers	25 (15.9)	13 (6.7)	
Ex-smokers	84 (53.5)	18 (9.4)	
Never-smokers	48 (30.6)	162 (83.9)	
Tobacco in pack-years	29.4	14.7	0.014
Respiratory symptoms			
Asthma history	4 (2.9)	6 (3.8)	NS
Wheezing	7 (5.1)	6 (3.8)	NS
Rhinitis	18 (15.2)	29 (19.7)	NS
Dyspnoea level 2 and above	22 (15.2)	49 (26.8)	0.011
Chronic sputum	28 (20.3)	16 (10.3)	0.016
Morning cough	21 (17.8)	12 (8.2)	0.018
Total IgE (kUI/l; mean $\pm$ SD [range])	98.1 $\pm$ 212.1 [1.9–2000]	74.6 $\pm$ 198.3 [1.9–2000]	0.018
Positive Phadiatop test	22 (13.9)	20 (10.3)	NS

Values are significant at $P \leq 0.05$.

Values in parentheses are percentages.

men (98.1 ± 212.1 kUI/l) than in women (74.6 ± 198.3 kUI/l ($P = 0.018$)). There were 42 (11.9%) subjects with a positive Phadiatop test, 302 negative, and the Phadiatop test was uncertain in 2.27% of subjects ($n = 8$). The proportion was similar in both genders (13.9% in men vs 10.3% in women). IgE levels were not associated with age. Subjects with a positive Phadiatop test were younger than the others (72 ± 5 vs 75 ± 6).

Univariate analysis

An univariate analysis has been performed to study total IgE levels and the proportion of positive Phadiatop tests in subjects according to the presence or absence of rhinitis, asthma and chronic sputum (Table 2).

The highest total IgE levels were observed in asthmatic subjects. There was no difference according to the

association or not of rhinitis to asthma (211.3 ± 315.7 vs 229.3 ± 358.9). The lowest levels were in subjects with chronic sputum; these levels did not significantly differ from normal subjects (47.1 ± 56.4 vs 56.2 ± 73.9).

The proportion of positive Phadiatop tests was significantly higher ($P < 0.001$) in subjects with asthma and/or rhinitis. Nevertheless as for total IgE, no difference was observed according to the association of rhinitis to asthma. Among the 24 subjects with only chronic sputum, no one had a positive Phadiatop test.

The association of total IgE with smoking was studied separately in men and women because of the great differences in smoking habits. In both genders, smokers had the highest rates of total IgE (KUI/l) (150 vs 98 for ex-smokers and 74 for never smokers among men, 211 vs 55 and 66 among women). No association was found between Phadiatop and smoking in both the genders.

Multivariate analysis

Multiple linear regression was performed with $\log_{10}$ IgE values as a dependant variable and age, Phadiatop test, smoking (smokers vs non-smokers and ex-smokers vs non-smokers), and respiratory symptoms independently in men and in women for smoking (Table 3). In men, a significant relationship was observed between IgE values and Phadiatop test ($P < 0.001$), asthma history ($P = 0.002$), and smoking (smokers vs non-smokers; $P = 0.019$). Association was limited with age. In women, total IgE was only associated with Phadiatop test.

A logistic regression analysis was used to assess the association between Phadiatop test and the same independant variables in both genders (Table 4), with no association having previously been observed between gender and Phadiatop by univariate analysis. Significant relationship was found with total IgE ($P = 0.001$, OR = 1.01, 95% CI 1.00–1.01), rhinitis ($P = 0.003$, OR = 4.56, 95% CI 1.66–11.95) and asthma history without chronic bronchitis ($P = 0.01$, OR = 16.46, 95% CI 1.98–136.86). No relationship was found with smoking, age and gender.

Discussion

Total IgE was significantly related to asthma and smoking in men, but related to Phadiatop in both

Table 2. Total IgE and Phadiatop according to asthma, rhinitis and chronic sputum: univariate analysis

	Rhinitis (n = 37)	Asthma and/or wheezing (n = 12)	Asthma, wheezing and rhinitis (n = 5)	Chronic sputum (n = 24)	Free of asthma, wheezing, rhinitis and chronic sputum (n = 174)
IgE [kUI/l; mean $\pm$ SD (range)]	71.8 $\pm$ 89.7 (2.3–388)	229.3 $\pm$ 358.9 (1.9–1243)	211.3 $\pm$ 315.7 (3.7–755)	47.1 $\pm$ 56.4 (1.9–202)	56.2 $\pm$ 73.9 (1.9–377)
Phadiatop test (percentage positive test*)	25.7	41.7	40.0	0.0	7.06

* $P < 0.001$.

Table 3. Multiple linear regression in men and women with total serum IgE ($\log_{10}$) as dependent variable

	β -Value	CI (95%)	P-value
Men*			
Age	0.01	-0.00 to 0.03	0.055
Phadiatop test	0.57	0.31 to 0.83	<0.001
Asthma history	0.83	0.31 to 1.35	0.002
Smokers vs non-smokers	0.32	0.05 to 0.60	0.019
Ex-smokers vs non-smokers	0.14	-0.05 to 0.33	0.153
Women†			
Age	-0.00	-0.01 to 0.01	0.810
Phadiatop test	0.51	0.20 to 0.82	0.001
Asthma history	0.19	-0.28 to 0.67	0.423
Smokers vs non-smokers	0.03	-0.35 to 0.42	0.862
Ex-smokers vs non-smokers	0.03	-0.26 to 0.31	0.838

Adjusted R^2 : R-squared for the regression, adjusted for degrees of freedom;
 * adjusted $R^2 = 0.22$; †adjusted $R^2 = 0.06$.

β -Value: estimated coefficient of regression.

CI: 95% confidence interval for the coefficient.

P-value: statistical significance was set a limit of $P \leq 0.05$.

Table 4. Logistic regression with Phadiatop test as dependent variable

Pseudo $R^2 = 0.24$	OR	CI (95%)	P-value
Sex	0.53	0.18 to 1.55	0.246
Age	0.94	0.86 to 1.03	0.193
Smokers vs non-smokers	0.71	0.14 to 3.53	0.672
Total IgE	1.01	1.00 to 1.01	0.001
Asthma history without chronic bronchitis	16.46	1.98 to 136.86	0.010
Rhinitis	4.56	1.66 to 11.95	0.003

Pseudo R^2 : Log-likelihood value on a scale of 0–1 (1 corresponds to perfect prediction).

OR: estimated odd's ratio.

CI: 95% confidence interval for the OR.

P-value: statistical significance was set a limit of $P \leq 0.05$.

genders. A positive Phadiatop test was not related to gender and smoking but significantly associated with total IgE, asthma and rhinitis. Our study demonstrates persistence of respiratory allergies after age 65 years and confirms an association between smoking and IgE level independent of allergic reactivity to common allergens for elderly people.

Elderly people are a select population and the respiratory diseases studied in this survey, such as asthma and smoking had a role in mortality in younger subjects. Thus, a selection bias related to survivors cannot formally be ruled out. Another information bias not easily avoidable in elderly people is that 'potential cognitive impairment can lead the subjects to give approximate responses because of memory problems'.

Our survey was based on a random sample of subjects who accepted to undergo venous blood withdrawal. Although bias could result from differential selection, our volunteers did not differ from other subjects with regard to age, gender, smoking, asthmatic status, rhinitis and chronic bronchitis.

The use of epidemiological questions to identify asthma in the elderly can be discussed. It is well known that asthma in the elderly is difficult to establish because cardiac diseases are often associated with senescence. The questions used in the study, had been previously validated taking the bronchial hyperresponsiveness as the reference in a sample aged between 18 and 64 years. Direct questions had a high specificity (97%), but only a 43% sensitivity. Identification of cases is often based on symptoms reported by patients (18). In a group of subjects aged 55 years and over, asthma was diagnosed only with the reversibility to Salbutamol. More than 41% had a reversibility test while only 7% of them received adequate treatment. Asthma is thus probably under-diagnosed and undertreated in the elderly (19).

Although it is commonly acknowledged that IgE (9) and skin reactivity (20) decrease with age, we observed a high range of IgE values including high IgE levels despite a mean of age more than 70 years in our cohort. IgE level was significantly higher in males than in females. In a representative sample of subjects aged 8–73 years, we found significantly higher serum IgE levels in males than in females. Nevertheless IgE-adjusted mean values for subjects aged 65 years and more, were lower than in the Paquid cohort (21). In the Tucson cohort, level of IgE in males > 55 years of age, was twice that in the females (2).

Allergic inflammation of the upper and lower airways could be a continuum of disease (22). In our survey, asthmatic subjects had higher total IgE levels than those with rhinitis. In contrast, the lowest levels were observed in subjects with chronic sputum and those without respiratory symptoms. Recently, epidemiologic evidence for asthma and rhinitis comorbidity had been raised (23). Our results showed the presence of both rhinitis and asthma in some elderly subjects. We used the Phadiatop test to measure the concentration of specific serum IgE against aeroallergens. The test is well characterized and has been used in previous surveys (24, 25). Contrary to total IgE, positive Phadiatop was not associated with gender but significantly with asthma and rhinitis. The proportion of subjects with a positive Phadiatop test was similar among subjects having both asthma and rhinitis than those with asthma alone.

A high concordance of total serum IgE but not to specific allergens when measured by a radioallergosorbent test (RAST) in twins has been shown (26), suggesting that total IgE is genetically determined, while sensitization could be environmentally determined (27). This difference could explain that despite a weak association between total IgE and rhinitis, we found a strong relationship between Phadiatop and asthma and rhinitis.

There are few data on smoking in elderly. At this age, a high proportion of people are already dead and there is a risk of underestimating the importance of smoking in survivors. In the cohort of British doctors, 41% of smokers have died before age 70 years (28). In the PAQUID cohort, 72.5% of men had smoked (16.7%

were current smokers and 55.8% former smokers). The proportion of current smokers decreased with age both in men and women, but at the same time, the proportion of former smokers remained constant. A potential bias of misclassification of former smokers as never smokers cannot be excluded (29). A small percentage of misclassified former smokers may bias the estimated relative risk of mortality associated with current smoking.

We found a significant correlation between IgE and smoking with separate analyses in men and women, because of the great differences in smoking habits. Jarvis et al. (4) reported a significant relationship between smoking and specific IgE among younger subjects. We did not observe any such association between positive Phadiatop test and smoking. Higher values of IgE were found in current smokers compared with non-smokers, regardless of skin test reactivity (21). Data from the Tucson cohort also showed a negative association

between smoking and skin test reactivity (8, 30). In the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA) study, a significant relationship was found between active and passive smoking with total IgE, independent of skin test response (31). Higher IgE levels in smokers compared with non-smokers may be due to the change in regulatory mechanisms of the IgE synthesis or increase of specific IgE related to frequent infections of smokers airways. Nevertheless at this time, induction of specific IgE antibodies against tobacco in smokers could not been proved (27).

In conclusion, despite modifications of immunological status related to age, our study demonstrates that respiratory allergies, especially asthma and rhinitis are not uncommon at this age. Like in other age groups, smoking appears to be associated with high levels of IgE but not to allergic reactivity to common allergens.

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