Persistence of atopic effects on airway calibre and bronchial responsiveness in older adults

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Abstract

Background: the relationships between atopy and chronic airflow obstruction and bronchial hyper-responsiveness in adults are unclear. We measured airways calibre (FEV₁), bronchial responsiveness, eosinophil count and total serum IgE in a random population sample of adults aged 45 years or older.

Methods: Caucasian adults (n = 783) were selected from the practice lists of local general practitioners using random number tables. Responders to a postal questionnaire were invited to attend for venous blood sampling and methacholine challenge (Newcastle dosimeter method).

Findings: the questionnaire response rate was 92.3% (723 subjects); 62.5% of subjects invited to attend did so. Attendees were slightly younger than the whole study population, but otherwise representative. Methacholine challenge was completed by 208 subjects. Geometric mean IgE level was higher in current smokers; both IgE and eosinophils were raised in subjects reporting asthma. Multiple regression showed a negative independent relationship between age- and sex-standardized eosinophils and baseline FEV₁ and a positive relationship between standardized IgE score and level of bronchial responsiveness. Separate analysis of subjects aged <65 and ≥65 years showed that these relationships were only significant in older subjects.

Interpretation: airways calibre and level of bronchial responsiveness are associated with measures of atopy in older adults. Atopy should not be overlooked as a factor in elderly patients with asthma or chronic airflow obstruction.

Keywords: atopy, bronchial hyper-responsiveness, obstructive airways disease, older people

Introduction

There is a strong link between asthma and atopy in children and young adults, but the relationship of atopy to asthma and chronic airflow obstruction in older adults is less clear. The suggestion that an inherited atopic tendency may predispose to development of chronic lung disease in smokers (the 'Dutch hypothesis' [1]) has been extensively investigated, with mixed results. One confounding factor is the relationship between cigarette smoking and raised serum immunoglobulin E (IgE), seen even in non-atopic smokers [2].

We measured total serum IgE and eosinophil count in an age-stratified random population sample of adults and elderly subjects, to assess the relationships of these measures of atopy with airways calibre (FEV₁) and bronchial responsiveness.

Methods

Population sampling

The study was approved by Central Manchester Health Authority ethical committee. A random sample of adults aged 45 and over was selected using random number tables from practice lists of local general practitioners. Confused and housebound patients were excluded, as were non-Caucasians (because of inter-racial differences in bronchial responsiveness [3]) and those with psychiatric illness or malignant disease. During the last months of recruitment, higher numbers of older adults were included by discarding every second person selected under the age of 70 years.

Subjects received an explanatory letter and a questionnaire, regarding treatment for asthma and chronic bronchitis, smoking history, respiratory symptoms,
ischaemic heart disease and current medications. Exclusion criteria for methacholine challenge were history of ischaemic heart disease and use of medications influencing the outcome of bronchial challenge (oral steroids, anticholinergic drugs and oral or topical \( \beta \)-blockers).

Subjects not excluded from methacholine challenge were invited to attend and requested to refrain from taking caffeine-containing drinks for 12 h beforehand. Those using bronchodilators were requested to avoid using these for 12 h (inhaled preparations), 24 h (oral medications) or 48 h (sustained-release preparations). Attendance was delayed for 6 weeks following upper respiratory tract infection or exacerbation of wheezing.

Subjects not responding after 4–6 weeks were sent a reminder and second copy of the questionnaire, followed 1 month later by a second reminder and abbreviated questionnaire. A random sample of persistent non-responders thought to still be living within the area was contacted by telephone or home visit and asked to complete the abbreviated questionnaire.

Bronchial challenge

A 12-lead echocardiograph was performed and those with evidence of ischaemia excluded from methacholine challenge. Baseline pulmonary function (mean of best six reproducible FEV\(_1\) readings) was measured by portable spirometer (Compact, Vitalograph, Buckingham, UK). Subjects with baseline airflow obstruction (FEV\(_1\) < 60% predicted [4, 5]) were also excluded from methacholine challenge.

Methacholine challenge was performed by the Newcastle dosimeter technique [6, 7]. Briefly, seated subjects, wearing a noseclip, inhaled sequential doubling doses of methacholine at 5 min intervals from a nebuliser attached to a microprocessor-controlled dosimeter. Spirometry was repeated before each dose (mean of three reproducible readings). The test continued until either a total cumulative dose of 6.4 mg methacholine had been inhaled or the subject developed bronchoconstriction sufficient to produce a 20% fall from baseline FEV\(_1\).

All subjects developing a 20% fall in FEV\(_1\) were given 1 mg of inhaled terbutaline (Bricanyl, Astra Pharmaceuticals, Kings Langley, UK) via a metered-dose inhaler and spacer device (Nebuhaler, Astra Pharmaceuticals) and remained within the department until FEV\(_1\) increased to within 10% of baseline.

Measures of atopy

Prior to methacholine challenge, 15 ml of venous blood was taken for analysis of eosinophil count and total IgE. IgE was measured by the paper radioimmunosorbent test method and reported in international units (IU) per ml. For 46 subjects the laboratory reported an IgE level < 5 IU/ml; to permit analysis these were given the value of 0.1 IU/ml. Differential eosinophil counts were estimated using a Coulter counter.

Data analysis

The result of methacholine challenge was expressed as methacholine dose required to produce 20% fall from baseline FEV\(_1\) (PD\(_{20}\)). The slope of the dose-response curve (DRS), was also calculated for all subjects [8]. Because a small number of subjects had an increase in FEV\(_1\) during the bronchial challenge, a constant of 0.43 was added to all calculated DRS measurements, eliminating negative slopes prior to logarithmic transformation [8]. Values of PD\(_{20}\), DRS, serum IgE and eosinophil count were log-transformed to achieve normal distribution.

Since eosinophil counts and serum IgE levels are dependent on age and sex [9–11], further analysis was performed using age- and sex-standardized ‘Z-scores’ [12]. The Z-score indicates the number of standard deviations by which each serum IgE or eosinophil count differs from the mean value of the appropriate sex and age group (45–54, 55–64, 65–74 and >75 years).

In order to avoid the age and height bias associated with the expression of FEV\(_1\) as percent of predicted values, baseline FEV\(_1\) for multiple regression to assess factors associated with bronchial responsiveness was expressed as standardized residuals [13]. These were calculated as: (recorded value-predicted value)/residual standard deviation about the regression equation used to calculate the predicted values [14].

The prediction equations used for the calculation of standardized residuals were derived from British urban Caucasian adults over an age range comparable to that in the current study [15].

Smoking habit was quantified as number of pack-years smoked, where 1 pack-year = 20 cigarettes daily for 1 year.

Subgroups were compared by two-sample \( t \)-test and \( \chi^2 \)-test. Multiple regression was used to investigate relationships between measures of atopy and pulmonary function. Statistical analysis was performed using the program Ecstatic (SomeWare in Vermont, VT, USA). In all cases significance was defined at the 5% level.

Results

Response rate

Of 783 eligible subjects contacted by post, 723 returned a questionnaire (response rate 92.3%). Of the 508 subjects returning sufficient information to determine eligibility for methacholine challenge, 113 were excluded because of ischaemic heart disease or interacting medications. The remaining 395 were invited to attend: 247 did so (62.5% of those invited;
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31.5% of total study population). Attenders were slightly younger than the remaining study population (attenders 64.5 years, study population 66.1 years; \( P = 0.02 \), but were representative in terms of sex distribution, reported asthma and bronchitis and smoking habits.

**Sample characteristics**

Of the 247 attenders, one could not perform reproduce spirometry, one declined bronchial challenge, two had echocardiograph abnormalities and 26 had baseline FEV\(_1\) <60% predicted. Thus, 217 subjects attempted methacholine challenge: nine failed (fatigue, cough or inability to perform reproducible spirometry) and 208 provided satisfactory results. Serum IgE measurements were available for 235 subjects and eosinophil counts for 231; missing data represent subjects declining blood tests and problems with sample transport or analysis.

One hundred and eighteen (56.7%) of those completing bronchial challenge were women. Sixty (28.8%) were current smokers and 84 (40.4%) ex-smokers. Eighteen (8.7%) reported asthma and 28 (13.5%) bronchitis; a further nine (4.3%) reported both asthma and bronchitis. The mean age was 63.7 years (range 45-86). Thirty-nine (18.8%) had chronic airflow obstruction (defined as FEV\(_1\)/FVC \(\leq 0.7 \)) for subjects aged <65 years; while for those aged \(\geq 65 \) a predicted FEV\(_1\)/FVC was calculated as described by Enright et al. [5]. One hundred and forty-eight subjects (71.1%) achieved a PD\(_{20}\), 49 (23.5%) had increased bronchial responsiveness (defined as PD\(_{20}\) \(\geq 100 \) \(\mu \)g methacholine [16, 17]).

One hundred and thirty-two (26.0%) of the 508 subjects completing the full questionnaire reported atopy (hay fever, contact dermatitis or eczema) and a further 89 reported atopy in a first-degree relative.

**Mean serum IgE and eosinophil levels**

The geometric mean serum IgE was 9.76 IU/ml (SD 2.13, \( n = 233 \)); 33 subjects had levels falling above the laboratory 'normal' range (<100 IU/ml). The geometric mean eosinophil count was 0.13 \(\times 10^3\)/l (SD 1.8, \( n = 231 \)); six subjects had results above the 'normal' range quoted by the measuring laboratory (0.04-0.4 \(\times 10^3\)/l).

Geometric mean IgE was lower in never-smokers [3.85 IU/ml (SD 14.60, \( n = 77 \)] than in ex-smokers [12.13 IU/ml (SD 7.85, \( n = 89 \); \( t = -3.06, P = 0.002 \)] or current smokers [21.18 IU/ml (SD 33.79, \( n = 68 \); \( t = -3.89, P = 0.0001 \)]. The difference between ex- and current smokers was not significant. There was a dose-response relationship between pack-years smoked and log IgE level, with significant linear correlation (\( r = 0.22, P < 0.001, n = 221 \)). Eosinophil count was not related to smoking habit.

Subjects reporting asthma had higher geometric mean IgE Z-scores [asthmatics: 0.36 (SD 0.77, \( n = 36 \), non-asthmatics: -0.07 (SD 1.00, \( n = 199 \); \( t = -2.94, P = 0.003 \)] and eosinophil Z-scores [asthmatics: 0.46 (SD 1.07, \( n = 35 \), non-asthmatics: -0.08 (SD 0.95, \( n = 195 \); \( t = -2.79, P = 0.005 \)]. Subjects reporting bronchitis also had higher mean IgE Z-scores [bronchitis: 0.25 (SD 0.80, \( n = 56 \), no bronchitis: -0.08 (SD 1.03, \( n = 179 \); \( t = -2.51, P = 0.01 \)]. In contrast, there was no difference in eosinophil Z-scores in subjects reporting bronchitis or in IgE and eosinophil Z-scores in those reporting personal or family history of atopy.

**Factors associated with baseline lung function**

Multiple regression was used to examine relationships between measures of atopy and baseline FEV\(_1\) (Table 1). Eosinophil Z-score showed an independent negative relationship with baseline FEV\(_1\); the weaker relationship between IgE Z-score and FEV\(_1\) failed to reach statistical significance. The square of the coefficient of multiple regression (\( R^2 \)) was 0.61. To assess whether the relationship between eosinophil count and FEV\(_1\) was present in both asthmatic and non-asthmatic subjects, an interaction term for the inter-relationship between eosinophils and reported asthma was added to the regression. This removed the relationship between eosinophils and FEV\(_1\), but the interaction term itself showed a significant negative association with FEV\(_1\) (\( B = -0.074, SE = 0.028, P = 0.007 \)), suggesting that the relationship between eosinophils and FEV\(_1\) was stronger in subjects reporting asthma. This was confirmed by repeating the regression calculation with the omission of subjects reporting asthma; when this was done eosinophils were no longer significantly related to FEV\(_1\).

Similarly, the effect of age on the relationship between eosinophils and FEV\(_1\) was investigated by the addition of an interaction term for the relationship between eosinophil count and age. This again removed the independent relationship between eosinophils and FEV\(_1\), but the interaction term itself showed a significant negative association with FEV\(_1\) (\( B = -0.001, SE = 0.0005, P = 0.008 \)), suggesting that the relationship between eosinophils and FEV\(_1\) was stronger in older subjects. To confirm this, the regression was repeated separately for subjects aged <65 and \(\geq \)65 years. This showed that there was no relationship between eosinophils and baseline FEV\(_1\) in the younger group (\( n = 118 \), but a significant negative relationship in those aged 65 and over (\( n = 90 \)).

**Factors associated with nonspecific bronchial responsiveness**

Regression analysis was performed with log DRS as dependent variable (\( R^2 = 0.39 \); Table 2). Baseline FEV\(_1\) was the strongest predictor of bronchial
Table 1. Factors associated with baseline FEV₁: multiple regression

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient (B)</th>
<th>Standard error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (m)</td>
<td>3.438</td>
<td>0.515</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pack-years smoked</td>
<td>-0.008</td>
<td>0.002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.033</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex*</td>
<td>0.348</td>
<td>0.099</td>
<td>0.0005</td>
</tr>
<tr>
<td>Z-score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>-0.091</td>
<td>0.036</td>
<td>0.01</td>
</tr>
<tr>
<td>IgE</td>
<td>-0.066</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Asthma b</td>
<td>-0.185</td>
<td>0.10</td>
<td>0.07</td>
</tr>
</tbody>
</table>

n = 211; R² = 0.61.
*1 = female, 2 = male.
bAs reported by patient: 1 = yes, 2 = no.

responsiveness, but IgE Z-score was also found to have an independent positive relationship with log DRS. An interaction term for the relationship between IgE and reported asthma was not significantly associated with log DRS; similarly, removal of asthmatic subjects from the regression did not affect the relationship between log IgE and log DRS.

Inclusion of an interaction term for age and IgE removed the independent relationship between IgE and log DRS; the interaction term itself showed a significant association with log DRS (B = 0.0025, SE = 0.001, P = 0.01), suggesting that the relationship between IgE and log DRS was stronger in older subjects. This was confirmed by separate analysis of younger and older subjects, which revealed that IgE was significantly associated with bronchial responsiveness only in those aged 65 and over.

Discussion

Our results show an association between baseline FEV₁ and eosinophil count: this confirms the results of other population surveys of lung disease [9, 18-24] and suggests a role for eosinophil-mediated airways inflammation in development of chronic airflow obstruction. Only one population study has failed to show any relationship between FEV₁ and measures of atopy, and this was a study that excluded asthmatic individuals [25]. As in a previous study [21], removal of self-reported asthmatic subjects from the analysis eliminated the relationship between eosinophil count and FEV₁. The relationship between baseline FEV₁ and total IgE level failed to reach significance in this population, although a significant association has been reported by others [9, 19-24].

Our results also show a relationship between bronchial responsiveness and IgE, but not eosinophil count. Other population surveys have also reported associations between bronchial responsiveness and eosinophils [26], IgE [27] or both [28, 29], although some have contradicted this [22, 30, 31].

We have, however, confirmed that smokers have elevated serum IgE levels. This relationship has been noted previously, but not explained [2, 24, 32-34]. Smoking increases the permeability of the bronchial...
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mucosa and so could increase the access of antigens to lymphoid tissue, enhancing sensitization to allergens [33]. Alternatively, components of cigarette smoke may affect stages of the immune response. Although several authors have also reported eosinophilia in current smokers [33, 35, 36], a relationship was not found in this study.

The raised serum IgE and eosinophils seen in subjects reporting asthma is not surprising [12, 21] and has been noted even in elderly asthmatic subjects [37]. It is of interest that subjects reporting atopy did not have raised IgE or eosinophil levels in our study. This may be the result of over-reporting of atopy: a previous study has reported the results of skin tests, IgE and eosinophils as showing only weak correlation with questionnaire reports of allergy [9].

Our finding that measures of atopy are more strongly associated with bronchial responsiveness and airflow obstruction in older adults is surprising and contradicts accepted teaching. Other studies of older adult populations have shown relationships between IgE and airways calibre [32] and between IgE, eosinophils and bronchial hyper-responsiveness [28]. However, the prevalence of positive skin tests decreases with age [38] and in one population survey skin-test positivity was associated with bronchial hyper-responsiveness only in subjects aged less than 55 years [39]. Our results suggest that atopic mechanisms should not be overlooked as an aetiological factor in older adults with asthma or chronic airflow obstruction.

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Key points

- Bronchial hyper-responsiveness is strongly associated with asthma and atopy in young people, but this relationship has been thought to be less strong in older adults and elderly subjects.
- In an age-stratified random population sample of adults aged ≥45 years, eosinophil count was found to be associated with airways calibre and total IgE level with bronchial responsiveness. These relationships were both stronger in adults aged >65 years.
- Atopy should not be overlooked as a factor in elderly patients with asthma or chronic airflow obstruction.

References

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