Research Letters

Alpha 1 antitrypsin phenotypes and obstructive airway disease in subjects over 65 years of age: QUID R Cohort

SIR—Airflow obstruction, chronic obstructive pulmonary disease (COPD) and asthma are major worldwide causes of morbidity [1].

Aetiology of COPD results from a complex interaction between genetic and environmental factors [2]. The main genetic risk factor for COPD is alpha1 antitrypsin deficiency. The normal genotype of protease inhibitors (PIs) is M and the classic severe respiratory deficiency is associated with the Pi Z genotype. However, the role of Pi S allele in COPD remains unclear [3], regarding in particular the interaction between this phenotype and environmental factors on the one hand, and respiratory ageing on the other hand. To our knowledge, the relationship between Pi genotype and COPD has been studied in the adult population, but not in older persons who have been exposed throughout their lives to smoking, and other environmental exposures.

The aim of the present study was to analyse the association between Pi genotype and obstructive airway disease in subjects over 65 years of age.

Material and methods

Study population and data collection

A total of 2,104 Caucasian subjects aged 66–88 years, who lived at home in the suburb of Bordeaux (France), were selected from electoral rolls to take part in the study [4]. All the subjects were informed of the conditions related to the study and gave their written, informed consent.

The subjects were interviewed at home concerning their sociodemographic characteristics. A medical work-up was performed in a mobile unit. A standardised questionnaire concerning medical history, smoking and respiratory symptoms including dyspnoea grade [5] was administered then anthropometric and spirometric measurements were performed.

Spirometric measurements was needed to respond to validity criteria to be included in the analyses: for slow and forced spirometry, two measures at least had to be reproducible [differences between successive values of vital capacity, forced vital capacity (FVC) and forced expiratory volume in 1 S < 5%]; the highest values of FVC and FEV1 considered for analysis could not exceed the following more than 5% or 100 ml.

The study was approved by the University Hospital of Bordeaux ethics committee; however, they did not authorise the investigator to administrate a bronchodilatator challenge test in these aged participants.

To identify patients with an obstructive airway disease, we used the COPD definition proposed by GOLD in 2003 [6]: a ratio of FEV1/FVC<70%.

Severity of obstruction was defined as followed: at risk (normal spirometry and chronic symptoms), mild (FEV1 ≥ 80% predicted value), moderate (30 ≤ FEV1 < 80% predicted value) and severe (FEV1 < 30% predicted value).

Genetic analyses were done on blood samples. The genetic profile was divided into six categories: SZ, MZ, SS, MS, MM and ZZ.

Statistical analysis

The socio-demographic characteristics and genetic profile of the sample were described. To assess the specific risk linked to Pi genotype adjusting for each significant covariate in univariate analyses, a logistic regression was performed with airflow obstruction as the dependent variable. We performed two models: the first analysis was conducted in the whole sample and the second in subjects without history of asthma. The main explanatory variable was genetic profile classified as three categories: MM genotype as the reference category, subjects with at least one Z allele (only PI MZ heterozygous individuals, as no Pi ZZ was observed in our sample) and subjects with at least one S allele (heterozygous genotypes PiMS, PiSZ and homozygous for PiS) [3]. The other explanatory variables were age, gender, smoking history and body mass index. Odds ratio (OR) with 95% confidence interval (95% CI) was determined for each variable. A P < 0.05 was considered as significant. Analyses were performed using the SAS 9.1 statistical software.

Results

The study sample was composed of 801 participants with validated forced expiratory spirometries, including 370 men. The mean age of the population was 73 ± 4 years. In men, 8.7% were smokers and 34.9% non-smokers. In women, 5.8% were smokers and 83.7% never smokers. No significant difference was found between excluded subjects and those included in this study.

Prevalence of M variant was 81.2%, S variant 17.1% and Z variant 1.7%. According to GOLD criteria, airflow obstruction prevalence was 15.0%. Fifty-three percent of...
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subjects had mild obstruction and very few subjects (1%) were at a severe stage.

Airway obstruction was more frequent among males (62.5%) than females (37.5%) \((P = 0.0002)\).

Prevalence by genetic profile

The prevalence of airway obstruction was higher in subjects with genetic profile Z (38%) than those with M profile (15%). However, it was similar in subjects with S (14%) and those with M profiles (15%). So, there was no significant difference \((P = 0.08)\) between genetic profile and airway obstruction (Table 1).

The OR for airway obstruction showed a significantly increased risk for Pi SZ compared with Pi MM. However, this association relied on a very small number of individuals \((n = 3)\). The association with the other genotypes did not reach the statistical significance.

Multivariate analysis

Table 2 shows the adjusted OR of airway obstruction among subjects without history of asthma and among all participants. The Z genotype was significantly associated with higher risk of airway obstruction compared with the MM group independent of the potential confounders in the whole sample. In subjects without history of asthma; no significant association was observed \((P = 0.14)\) between genetic profile and airway obstruction but the Z and S genotypes seemed to have a higher risk than the MM group. In both groups, women were at lower risk than men and those with M profile seemed to have a higher risk than the MM group. The OR for airway obstruction showed a significant association \((P = 0.01)\) between the Z genotype and airway obstruction in spite of a greater OR in this subgroup. This result could be related to the lack of power of the study.

There are great variations in prevalence rates of COPD in elderly persons in the literature [7]. These variations are generally attributed to genetic and environmental factors. In our sample, the prevalence of airway obstruction was 15%. Anto et al. had found that the proportion of COPD was 30% in patients aged over 60 years [7].

Elderly people are a selected population and some of respiratory diseases or risk factors studied in this survey, such as asthma and smoking play a role in mortality among younger subjects. In addition to this selection by premature mortality, one limitation of the current study is the potential selection bias. Only 801 subjects with forced expiratory spirometers were considered as validated for analysis. However, there was no difference in age, smoking history and respiratory symptoms between the participants and those excluded.

The ethics committee did not allow us to use bronchodilator during the challenge test. So, even if COPD was related with smoking status, there is a possibility of misclassifying some cases with asthma and other diseases as COPD since detailed medical assessment was not performed on these subjects and a chest radiograph was not included in the protocol.

Curiously, we did not find any clear relationship between smoking habits and airway obstruction; only a slight tendency, other studies have shown similar results [8]. One reason for this could be the lower proportion of smokers and exsmokers in our sample than in the French active population: only 39% in our sample and more than 50% in the active population [9]. Some smokers and exsmokers die before age 65 from tobacco-related respiratory disease [10]. In this study, it should be remembered that subjects in whom the effect of tobacco was the most severe had already died [11].

The prevalence of variant Z varies according to geographic location, indeed in Europe the frequency varies

**Table 1.** Airway obstruction according to genetic profile in a sample of French older adults: QUID R study

<table>
<thead>
<tr>
<th>Genetic profile</th>
<th>Airway obstruction, (n = 669) (%)</th>
<th>No airway obstruction, (n = 649) (%)</th>
<th>OR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>93 (80.2)</td>
<td>529 (81.4)</td>
<td>1</td>
</tr>
<tr>
<td>MZ</td>
<td>3 (2.6)</td>
<td>7 (1.3)</td>
<td>2.43 0.62–9.58</td>
</tr>
<tr>
<td>MS</td>
<td>17 (14.7)</td>
<td>108 (16.7)</td>
<td>0.90 0.51–1.56</td>
</tr>
<tr>
<td>SZ</td>
<td>2 (1.7)</td>
<td>1 (0.15)</td>
<td>11.35 1.02–126.4</td>
</tr>
<tr>
<td>SS</td>
<td>1 (0.9)</td>
<td>5 (0.8)</td>
<td>1.14 0.13–9.82</td>
</tr>
</tbody>
</table>

*By comparison to the MM genetic profile.

**Table 2.** Factors associated with airway obstruction by a multivariate logistic regression model in a sample of French older adults: QUID R study

<table>
<thead>
<tr>
<th>Factors</th>
<th>All respondents, (n = 765)</th>
<th>Subjects without history of asthma, (n = 697)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Gender (women versus men)</td>
<td>0.36 0.21–0.63</td>
<td>0.0003 0.38 0.21–0.65</td>
</tr>
<tr>
<td>Tobacco (versus lifetime non-smokers)</td>
<td>0.7000 0.35</td>
<td></td>
</tr>
<tr>
<td>Exsmokers</td>
<td>1.23 0.72–2.08</td>
<td>1.22 0.77–2.11</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.26 0.55–2.91</td>
<td>1.49 0.66–3.34</td>
</tr>
<tr>
<td>BMI (versus (\geq 21) kg/m²)</td>
<td>3.08 0.66–1.68</td>
<td>0.0002 2.27 0.85–6.01</td>
</tr>
<tr>
<td>For wheezing during the last 12 months</td>
<td>2.67 1.29–5.54</td>
<td>0.0070 2.48 1.04–5.88</td>
</tr>
<tr>
<td>Asthma history</td>
<td>4.82 2.40–9.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyspnœa</td>
<td>1.82 1.19–3.40</td>
<td>0.0500 3.05 0.85–10.88</td>
</tr>
<tr>
<td>Genetic Profile (versus MM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>0.80 0.43–1.48</td>
<td>1.04 0.57–1.86</td>
</tr>
<tr>
<td>Z</td>
<td>4.19 1.26–13.88</td>
<td>2.94 0.85–10.1</td>
</tr>
</tbody>
</table>

S, Pi MS, Pi SS, PiSZ; Z: PiMZ. OR, adjusted OR; CI, confidence interval.
between 0 and 30 per 1,000. In our study, the prevalence was 1.7%. This proportion is similar to that reported in the literature [12, 13].

In agreement with some previous studies [3, 14], the OR for airway obstruction in MZ heterozygote compared with MM genotype was 2.43 in our study. One limitation of the study is the fact that the genotype Z is very rare; however, 1 or 2 subjects different in each group could change the results. The OR for airway obstruction compared with the MM genotype was 11.35 for the SZ genotype. A meta-analysis on COPD in the group PiSZ showed a higher risk in this group compared with PiMM [3].

Comparisons of risk of airway obstruction between PiMM and PiMS showed no significant difference, other studies have shown similar results [3]. According to literature, the absence of association could be due to the use of a definition of COPD based on data from spirometry or after adjusting the smoking status [3].

In summary, our findings indicate that the Pi Z group may be more susceptible to the development of airflow obstruction than Pi MM. However, no significant association was observed between S genotype and airway obstruction.

Further studies including larger sample size will be required to determine the presence of the risk of airflow obstruction in the Pi S group.

Key points

- Alpha-1 antitrypsin is a major factor to chronic pulmonary disease independently of smoking in adults.
- Subjects aged 65–85 years old were included in this study.
- Obstructive airway disease was associated with genetic profile in older persons.

Conflicts of interest

None declared.

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References


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