SHORT REPORT

 α_1 Antitrypsin and the prevalence and severity of asthma

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In a random sample of children (aged 9–11 years; $n = 5629$), who were studied according to the ISAAC phase II protocol, heterozygosity of the α_1 antitrypsin (α_1 -AT) Pi genotypes MS or MZ, or low α_1 -AT plasma levels, were not associated with an increased risk of developing asthma. Asthmatics with low levels of α_1 -AT were particularly prone to develop airway hyperresponsiveness and reduced lung function.

Heterozygous α_1 antitrypsin (α_1 -AT) phenotypes have been suggested to contribute to the risk of developing asthma and atopic diseases in children¹ and adults.² Lack of an effective airway protease screen may contribute to the inflammatory processes characteristic of asthma in predisposed children, which may lead to an increased risk for the development of asthma, reduced pulmonary function, and signs of more severe symptoms of asthma and related atopic disorders.

The relation between the prevalence and severity of asthma and allergic disorders and Pi heterozygosity and α_1 -AT plasma levels, respectively, was studied in two large random samples of schoolchildren in eastern and western Germany.

METHODS

Using the ISAAC phase II study protocol, cross-sectional surveys addressing all fourth graders (aged 9–11 years) via parental questionnaires (including the ISAAC core questions) at randomly selected schools in Dresden ($n = 3668$) and Munich ($n = 3830$), Germany, were performed in 1995 and 1996; results are described in detail elsewhere.³ A child with a reported doctor's diagnosis of asthma or recurrent asthmatic or spastic bronchitis was classified as having asthma. Among asthmatics, the frequencies of asthmatic symptoms and episodes, medication, and hospital admissions were assessed.

Plasma α_1 -AT concentrations were measured using the rate-nephelometric immunochemistry system (ICS, Arrayi, Beckman Instruments, Fullerton, CA, USA). Genotyping of α_1 -AT deficiency alleles PiZ and PiS was done using polymerase chain reaction techniques.⁴ Plasma specimens not typing for PiZ or PiM were defined as having other Pi genotypes.

As the lung function measurements and the bronchial challenge were time consuming, they were offered only to a random subsample of children in Dresden ($n = 1999$) and Munich ($n = 2019$). Bronchial hyperreactivity (BHR) was assessed as a fall in FEV₁ of at least 15% after challenge with a 4.5% hyperosmolar saline solution. Atopy assessment and lung function measurement is described in detail elsewhere.³

Statistical analysis

The analysis was restricted to children with German nationality, which reflects ethnicity rather than place of birth in Germany. Wilcoxon tests, t tests, and χ^2 tests were

computed for bivariate comparisons. The cut-off limit for low levels of α_1 -AT was defined as the 5th centile (≤ 116 mg/dl) of the population distribution. Baseline pulmonary function values were computed as percent predicted standardised for age, height, and weight separately for girls and boys.³

RESULTS

The participation rates of the two study centres are reported in detail elsewhere.³ Overall, 6399 parents of the 7498 addressed children completed the questionnaire (85.3%), and 5629 of the participants were of German origin (87.8%) (median age 10 years, range 9–13 years). Both lung function measurements and blood samples were obtained for 48.8% of the eligible German children.

Prevalence rates for symptoms and diagnoses of asthma, allergic and respiratory disorders, or a family history of asthma or hay fever were not significantly associated with Pi genotype, or average plasma levels of α_1 -AT. The asthma prevalence was 4.9% ($n = 4$) for PiMZ, 6.5% ($n = 8$) for PiMS, and 9.2% ($n = 279$) for other genotypes. Only the prevalence of BHR was increased among subjects with PiMZ (27.8%, 10/36) versus PiMS (19.6%, 11/56) and other genotypes (16.9, 227/1346), being in line with the increased prevalence of BHR among children with low levels of α_1 -AT (≤ 116 mg/dl v >116 mg/dl) in comparison to children with normal α_1 -AT values (23.1%, 12/52 v 16.9%, 234/1382) in the total sample. However, these differences did not reach statistical significance, which may be due to the small numbers in subgroups. No consistent association between plasma levels of α_1 -AT and atopic sensitisation was observed.

Among children with asthma or BHR, low levels of α_1 -AT were related to significant decrements in FEV₁ and MEF₅₀ (table 1). Asthmatics with PiMZ genotype showed similar, though non-significant, reductions in lung function compared with PiMS or other genotypes (mean levels of % predicted (SE): MEF₇₅: 85.9 (19.9) v 101.2 (16.4) v 94.5 (18.2); MEF₅₀: 84.5 (35.1) v 99.0 (12.9) v 91.8 (23.2)).

The severity of asthma, assessed as the frequency of symptoms, hospital admissions, days missing from school, and asthma medication intake, was not affected by low α_1 -AT plasma levels. Only BHR was increased among asthmatic children with low levels of α_1 -AT compared to asthmatics with normal levels (60%, 3/5 v 35%, 43/123). However, the difference did not reach statistical significance, probably because of the small numbers in the subgroups. The number of asthmatics with PiMZ genotype ($n = 4$) prohibited further analysis in relation to genotype.

DISCUSSION

The findings of this study suggest that the risk of developing asthma or hay fever is not increased in children with α_1 -AT Pi heterozygosity or low α_1 -AT plasma concentrations. Low levels of α_1 -AT were related to impaired lung function among children with asthma; however, the number of children in the subgroups was relatively small (table 1). The observed

Table 1 Pulmonary function† in children with asthma or BHR according to presence or absence of low plasma level of α_1 -AT (≤ 116 mg/dl)

	α_1 -AT ≤ 116 (n=16)‡	α_1 -AT >116 (n=341)‡
FVC	95.5 (3.0)	100.3 (0.6)
FEV ₁	92.6 (2.9)*	98.2 (0.6)
FEV ₁ /FVC	97.0 (1.3)	98.2 (0.4)
PEF	88.4 (4.2)	97.1 (1.0)
MEF ₇₅	87.5 (4.1)	94.6 (1.0)
MEF ₅₀	79.5 (6.8)*	92.1 (1.2)
MEF ₂₅	82.3 (6.2)	92.1 (1.8)
MMEF	82.9 (4.7)	92.0 (1.3)

†Pulmonary function adjusted for height, weight, and gender.

‡% predicted; least square mean (SE).

*p<0.05; †test in comparison to children with asthma or BHR and α_1 -AT >116 mg/dl.

relation to BHR may be spurious because of small numbers in the various categories. The association between atopy and low α_1 -AT was inconsistent.

Neutrophil elastase has been shown to be involved in bronchoconstriction and airway hyperresponsiveness,⁵ and the disruption of the elastic fibre network of the lung, thereby reducing elastic recoil.⁶ Thus, an imbalance of the elastase/ α_1 -AT levels in the lung may indeed contribute to airway inflammation and thereby to increased airway responsiveness and impaired lung function among asthmatic children. Findings among adults reporting an increased risk for BHR in subjects with both heterozygous genotypes and reduced α_1 -AT levels further support this notion.²

In conclusion, this study proposes that heterozygous Pi genotypes or low levels of α_1 -AT in plasma do not enhance the risk of children developing asthma or hay fever. The findings suggest, however, that an impaired α_1 -AT balance may potentially increase the vulnerability for decrements in lung function and BHR in children who already have asthma,

which needs to be confirmed or rejected by further investigations.

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