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Lung function in 30-year-old alpha-1-antitrypsin-deficient individuals

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Summary
Background: Alpha-1-antitrypsin (AAT) deficiency increases the risk of emphysema, especially in smokers. In 1972–1974, all 200,000 Swedish new-born infants were screened for AAT deficiency and individuals with severe (PiZZ) and moderate (PiSZ) deficiency have been followed-up regularly. The aim of the present study was to examine their lung function at the age of 30 years, comparing them to a group of age-matched control subjects (PiMM) recruited from the general population, and to compare current smokers with never-smokers.
Method: Static and dynamic spirometry, including TLC, FRC, RV, VC, FEV_1, K_{CO} and $D_{L,CO}$, was performed for all participants. All values were expressed as percentages of the expected values. FEV_1/VC was expressed both as percentage of the expected value and in absolute numbers.
Results: Four of 60 PiZZ, none of 19 PiSZ and 9 of 33 PiMM participating individuals were current smokers. All Pi groups had a normal mean FEV_1. The mean (SD) FEV_1/VC ratio was 75% (7.4) in the PiZZ smokers and 84% (5.5) in the PiZZ never-smokers ($p < 0.01$). The mean (SD) K_{CO} was 81 (13) in the PiZZ smokers and 99 (14) in the PiZZ never-smokers ($p < 0.05$).
Conclusion: AAT-deficient individuals identified by neonatal screening have normal lung function at the age of 30. The PiZZ smokers had changes in lung function that may be signs of early emphysema.

Introduction

Alpha-1-antitrypsin (AAT) is primarily synthesized in the liver. Its major function is to protect lung tissue elastin from neutrophil elastase-mediated destruction by irreversibly binding and inhibiting elastase.[1] AAT-deficient individuals have various degrees of loss of function

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depending on the protease inhibitor (Pi) phenotype. Severe AAT deficiency (PiZZ) increases the risk of developing emphysema and in PiZZ smokers, emphysema may occur as early as in the fourth decade of life[2] but the natural history of lung disease in AAT deficiency is still incompletely known. As for emphysema and chronic obstructive pulmonary disease (COPD) in general, dyspnoea is often the first symptom in patients with severe AAT deficiency, while wheezing has been shown to predict a decrease in lung function.[3]

The individuals with severe (PiZZ) and moderate (PiSZ) AAT deficiency in this study were identified in the Swedish neonatal AAT screening of 1972–1974.[4] The aim was to investigate the lung function in this cohort at 30 years of age, to compare with an age-matched control group (PiMM) from the general population, and to investigate whether pulmonary function within the cohort differs between smokers and non-smokers.

Material and methods

Subjects

From November 1972 until September 1974, all 200,000 Swedish new-born infants were screened for AAT deficiency, and 127 PiZZ, 54 PiSZ, 2 PiZ– and 1 PiS– subjects were identified. Five PiZZ children died early and four PiZZ individuals have been included after the screening. The present cohort of 128 PiZ (including two PiZ–) and 55 PiSZ (including one PiS–) AAT-deficient, 30-year-old individuals were invited to undergo pulmonary function tests at the Department of Clinical Physiology at the University Hospital, Malmö or at their local hospital.

Of 300 randomly selected control subjects from the Swedish population registry, 90 individuals had visited the Department of Respiratory Medicine, University Hospital, Malmö, for a previous study.[5] The control subjects were tested for AAT and six individuals, found to be heterozygotes, PiMZ, were excluded from further analysis. The remaining 84 PiMM subjects were invited to undergo pulmonary function tests at the Department of Clinical Physiology at the University Hospital in Malmö.

Information about smoking habits, including number of cigarettes per day and years of smoking, as well as records of wheezing and breathlessness, for all participants were obtained from a questionnaire, collected as previously reported.[5]

The study was conducted in accordance with the Helsinki Declaration, and approved by the Regional Ethical Review Board of Lund University, Sweden. All participants in the study gave their signed, informed consent.

Pulmonary function tests

Examinations were requested to be done according to a protocol, which included static and dynamic spirometry, i.e. total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and diffusing capacity for carbon monoxide ($D_{L,CO}$), including transfer coefficient (K_{CO}), forced expiratory volume in one second (FEV_1) and vital capacity (VC). FEV_1 and VC were measured before and 15 min after bronchodilation with either 1.0 mg terbutaline or 0.4 mg salbutamol. TLC and RV were measured in the majority of cases with body plethysmography, while the gas dilution technique was used in some subjects. Lung function tests, including calibration of the equipment, were performed according either to the European Respiratory Society (ERS) guidelines (the majority of cases, and including the examinations done in Malmö),[6] or to the American Thoracic Society (ATS) guidelines (few cases).[7]

Pulmonary function variables are expressed as percentages of the expected values and are computed using the European Coal and Steel Community summary equations.[8] When not otherwise indicated, values after bronchodilation are reported, i.e. for VC, FEV_1 and FEV_1/VC. FEV_1/VC is expressed both as percentage of the expected value and in absolute numbers (FEV_1/VC ratio).

Comparison of the results of the pulmonary function tests was made between the Pi subgroups and between the smoking subgroups, i.e. current, ex- and never-smokers.

Statistical analysis

Statistical analyses were carried out using SPSS 12.0.1 software. Continuous variables were analysed with ANOVA. The χ^2-test was used to analyse categorical values. Testing for normal distribution was done using the Shapiro–Wilks test.

Results

Participation and smoking history

The number of participants, their age and smoking history are presented in Table 1. Sixty of the 126 PiZZ, none of the 2 PiZ–, 19 of 55 the PiSZ and 33 of the 294 control subjects underwent pulmonary function tests. There was no significant difference in age between the AAT-deficient and the

Table 1 Response frequency, gender ratio, age and smoking history in the three Pi groups.

	PiZZ ($n = 60$)	PiSZ ($n = 19$)	PiMM ($n = 33$)
Gender, *n* (%) female	24 (40)	9 (47)	17 (52)
Age, years	31 (30–33)	31 (28–33)	31 (30–32)
Smoking habits			
Current smokers, *n* (%)	4 (7)	0 (0)	9 (27)
Ex-smokers, *n* (%)	4 (7)	3 (16)	4 (12)
Never-smokers, *n* (%)	52 (87)[a]	16 (84)	20 (61)[†]
Number of pack-years in ever-smokers	4.6 (0.4–8.1)	5.8 (1.5–12.0)	7.3 (0.2–17.8)
Age at which ex-smokers quit	22 (16–27)	23 (20–27)	23 (14–29)

Age, pack-years and age when quitting are expressed as mean (range).

[†] $p < 0.05$ compared to all AAT-deficient subjects.

[a] The sum of percentages in the PiZZ group does not equal 100 due to rounding up.