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Respiratory symptoms and lung function in 30-year-old individuals with alpha-1-antitrypsin deficiency

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Summary
Introduction: Individuals with severe alpha-1-antitrypsin (AAT) deficiency have a well-known risk of developing emphysema but it is not known at which age the first symptoms occur and lung function declines. The aim of this study was to examine the prevalence of smoking, respiratory symptoms and lung function at the age of 30 in AAT-deficient individuals (PiZ and PiSZ) identified by neonatal screening.
Material and methods: One hundred and seven PiZ, 45 PiSZ and 197 control subjects (PiMM) filled in a questionnaire regarding smoking habits and symptoms. Ninety PiZ, 40 PiSZ and 84 control subjects underwent spirometry including FEV_1 and FVC.
Results: Twenty-one percent of PiZ, 23% of PiSZ and 34% of PiMM subjects had smoked at some time ($p<0.05$). Sixty-five percent of PiZ, 55% of PiSZ and 35% of PiMM ever-smokers reported shortness of breath on exertion ($p<0.05$ PiZ vs PiMM). The mean FEV_1 was 101% predicted (95% CI 98–104) in PiZ, 101% predicted (95% CI 97–106) in PiSZ, and 96% predicted (95% 93–98) in PiMM individuals ($p<0.05$). There was no difference in mean FEV_1 when comparing ever- and neversmokers in the different Pi groups separately.
Conclusion: At the age of 30, the AAT-deficient individuals in this cohort report more symptoms than the control subjects. Smoking is less common in the cohort compared to controls. Their lung function is normal.

Introduction

Severe alpha-1-antitrypsin (AAT) deficiency (PiZ) increases the risk of emphysema, especially in smokers. The knowledge about when lung function starts to decline is sparse, but most PiZ life-time non-smokers may remain clinically healthy.[1] PiZ individuals also have an increased risk of liver disease, in children as neonatal cholestasis and in adults as cirrhosis and hepatocellular carcinoma.[2–4] In moderate deficiency (PiSZ) the risk of developing COPD is also increased but it is not known at which age symptoms occur and lung function starts to decline.[5]

The Swedish AAT deficiency screening was started in November 1972 and continued until September 1974 with

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the main purposes to study the natural history of lung and liver disease and to prevent lung disease. During this period, all Swedish newborn infants, 200 000 children, were screened for AAT, and those with severe (PiZ), and moderate (PiSZ) deficiency, have been followed every second year until the age of 18 and since then every fourth year.[3,6–8] The families were advised to stop smoking and/or protect the child from passive smoking. At 12 years of age and onwards, the AAT-deficient adolescents were advised not to start smoking.

The aim of this study was to examine the prevalence of respiratory symptoms, smoking habits and lung function in this cohort of AAT-deficient individuals at the age of 30.

Methods

Study population

The PiZ and SZ newborn children were identified by a neonatal AAT screening method in two steps. First AAT was measured from dried blood with transferrin as a reference and the level was determined by electroimmunoassay. If the serum concentration was less than 40% of the reference the Pi type was determined by crossed immunoelectrophoresis.[3]

Screening identified 127 PiZ, 2 PiZ-, 54 PiSZ and 1 PiS-subjects. Four PiZ children, who had neonatal liver disease, died early, but from different causes. Two of them died from liver cirrhosis and one died from aplastic anaemia, having liver cirrhosis at autopsy. The fourth one died in an accident. One PiZ child died from an anaphylactic shock and one PiSZ child died from a sudden infant death syndrome.

Due to the identification of unknown cases born in 1972–1974 there are now 128 PiZ (including two PiZ-) and 55 PiSZ (including one PiS-) individuals in the cohort. All these individuals were invited to participate in the follow-up at the age of 30. Since the screening was nationwide, they lived all over Sweden.

As a control group a random sample of 300 persons living in the southern part of Sweden (Skåne County) was drawn from the Swedish Population Registry. The control subjects were born from January 1973 to September 1974, and thus, if born in Sweden, had been screened for AAT deficiency and thus not having moderate or severe AAT deficiency. The level of AAT in blood was analysed by immune nephelometry on a Beckman–Coulter Immage and individuals with decreased AAT were phenotyped with iso-electric focusing and, if found to be PiMZ, excluded. All controls with normal levels of AAT in blood were assumed to be of normal phenotype (PiMM).

The study was approved by the Regional Ethical Review Board of Lund University, Sweden. All study participants gave their signed informed consent.

Questionnaire

A questionnaire, that was a modified version of the adult respiratory disease questionnaire used in epidemiological research,[9] was sent to all participants by regular mail. Non-responding participants were reminded twice by mail and then rung and interviewed by phone. The questionnaire included questions regarding smoking habits (age when starting, age of smoking cessation in ex-smokers, and average number of cigarettes per day during the time of smoking), respiratory symptoms (production of phlegm, wheezing, and shortness of breath when walking on flat ground) and occupation (including exposure to occupational dust, fumes or gas). The same questionnaire has been used at the previous checkups.[8,10]

Physical examination and dynamic spirometry

The AAT-deficient individuals were invited to undergo physical examination by a chest physician at their local hospitals. During the visit, dynamic spirometry, including FEV_1 and FVC, was performed. It was requested that lung function parameters were to be examined before and 15 min after the administration of inhaled $beta_2$-agonist (Bricanyl® 1.0 mg) and according to ERS guidelines.[11] The control subjects visited the Department of Respiratory Medicine at the University Hospital, Malmö, and performed dynamic spirometry including FEV_1 and FVC, before and 15 min after inhalation of a $beta_2$-agonist (Bricanyl® 1.0 mg). The results of lung function tests (FEV_1 and FVC) are expressed as percentage of predicted values according to the reference values of Berglund et al.[12] The FEV_1/FVC ratio is expressed as percentage. A positive reversibility test was defined as 12% and 200 ml increase of FEV_1 after inhalation of bronchodilator.

The clinical diagnoses, if any, in the AAT-deficient individuals were reported by their physician in a survey protocol, while the control subjects were interviewed by the study nurse during their clinical visit.

Statistical analysis

Comparison of categorical variables was performed with the χ^2 test. For continuous variables the 95% confidence

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

	PiZ ($n = 107$)	PiSZ ($n = 45$)	PiMM ($n = 197$)
Females, *n* (%)	46 (43)	22 (49)	106 (54)
Smoking habits			
Smokers, *n* (%)	7 (6.5)	5 (11.1)	30 (15.2)
Ex-smokers, *n* (%)	16 (15.0)	6 (13.3)	36 (18.3)
Non-smokers, *n* (%)	84 (78.5)	34 (75.6)	131 (66.5)*

*$p < 0.05$ compared to all AAT-deficient subjects.

intervals were estimated. The comparison of continuous variables were analysed by ANOVA. The p-values were considered significant at the <0.05 level. Statistical analysis was accomplished using SPSS 12.0.1 software.

Results

Questionnaire

Of the 128 PiZ individuals 107 (84%) completed the questionnaire, as did 45 (82%) of the 55 PiSZ individuals and 203 (68%) of the 300 control subjects. Six control subjects, proving to be PiMZ, were excluded from further analysis. Smoking habits are shown in Table 1. Life-time non-smokers were significantly more common among the AAT-deficient individuals than among the control subjects ($p<0.05$). Due to the small numbers of current and ex-smokers among the AAT-deficient individuals, further comparisons were made between ever- and never-smokers.

Tables 2 and 3 demonstrate the prevalence of respiratory symptoms in the Pi subgroups. The only significant difference between the Pi subgroups as a whole was the increased prevalence of production of phlegm in the PiSZ subjects when compared with the PiMM subjects ($p<0.05$). The PiZ ever-smokers reported a higher prevalence of shortness of breath on exertion than the PiMM ever-smokers ($p<0.05$) while the PiZ never-smokers reported a higher prevalence of wheezing than the PiMM never-smokers ($p<0.05$). All three respiratory symptoms were more common among the PiZ ever-smokers than among the PiZ never-smokers. In the PiMM subgroup, the prevalence of phlegm and wheezing, but not exertional dyspnoea, were significantly increased among the ever-smokers compared to never-smokers. Among the PiSZ individuals, no significant differences in prevalence of respiratory symptoms were found between the smokers and non-smokers.

Fifty-seven AAT-deficient subjects (38%) and 59 control subjects (30%) reported exposure to occupational dust, fumes or gas. Seventeen (50%) of 34 ever-smoking AAT-deficient and 25 (38%) of 66 ever-smoking PiMM subjects had been exposed to occupational dust, fumes or gas. Of these, 11 AAT-deficient subjects (65%) and 8 PiMM subjects (32%) reported shortness of breath on exertion ($p<0.05$). No significant differences were found in never-smokers.

Table 2 Prevalence of symptoms in the Pi subgroups.

	PiZ ($n=107$)	PiSZ ($n=45$)	PiMM ($n=197$)
Phlegm	18 (17%)	13 (29%)*	31 (16%)
Wheezing	33 (31%)	15 (33%)	41 (21%)
Shortness of breath	45 (42%)	21 (47%)	77 (39%)

*$p<0.05$ compared to PiMM subgroup.

Table 3 Prevalence of symptoms in ever- and never-smokers in the different Pi groups.

	PiZ	PiSZ	PiMM
Never/ever-smokers, n	84/23	34/11	131/66
Phlegm			
Never-smokers	11 (13%)	10 (29%)*	14 (11%)
Ever-smokers	7 (30%)‡	3 (27%)	17 (26%)‖
Wheezing			
Never-smokers	22 (26%)†	9 (26%)	19 (15%)
Ever-smokers	11 (48%)‡	6 (55%)	22 (33%)‖
Shortness of breath			
Never-smokers	30 (36%)	15 (44%)	54 (41%)
Ever-smokers	15 (65%)†,‡	6 (55%)	23 (35%)

*$p<0.01$ compared to PiMM never-smokers.
†$p<0.05$ compared to corresponding PiMM sub-groups.
‡$p<0.05$ compared to PiZ never-smokers.
‖$p<0.001$ compared to PiMM never-smokers.

Lung function tests and diagnoses

Spirometry was performed in 90 PiZ, 40 PiSZ and 84 PiMM individuals. The number of women was 37 (41%), 21 (53%) and 47 (56%) in each group, respectively. The results of the lung function tests are shown in Table 4. The control subjects were somewhat older than the AAT-deficient individuals ($p<0.001$). The AAT-deficient individuals had normal lung function, while the mean FEV_1 and FVC in the control subjects were somewhat lower than the expected values. There were no significant differences in the mean FEV_1/FVC ratios between the Pi subgroups.

Table 4 Age of study participants and results of lung function tests.

	PiZ ($n=90$)	PiSZ ($n=40$)	PiMM ($n=84$)
Age, years	30.5 (29.2–32.3)	30.5 (29.6–32.3)	31.1 (29.8–32.5)*
FEV_1, % predicted	101 (98–104)†	101 (97–106)†	96 (93–98)
FVC, % predicted	100 (97–103)‡	101 (97–104)‖	93 (91–95)
FEV_1/FVC, %	82 (80–83)	82 (79–84)	84 (83–85)

Age is expressed as mean (range) and lung function values as means (95%CI).
*$p<0.001$ compared to PiZ+PiSZ.
†$p<0.05$ compared to PiMM.
‡$p<0.001$ compared to PiMM.
‖$p<0.01$ compared to PiMM.

Table 5 Results of lung function tests in the smoking subgroups.

	PiZ	PiSZ	PiMM
Never/ever-smokers, *n*	73/17	30/9	52/32
FEV_1, % predicted			
Never-smokers	100 (97–103)	101 (96–106)	96 (93–98)
Ever-smokers	101 (93–109)	102 (91–112)	96 (92–99)
FVC, % predicted			
Never-smokers	99 (96–102)*	101 (96–105)*	92 (90–95)
Ever-smokers	103 (96–111)*	101 (94–109)	94 (91–96)
FEV_1/FVC, %			
Never-smokers	82 (80–84)	81 (79–84)	84 (83–86)
Ever-smokers	79 (76–83)	82 (75–88)	83 (81–86)

Lung function values are expressed as means (95%CI).
[a]Two PiZ and one PiSZ subject did not answer the questionnaire thus not revealing smoking status.
*$p<0.01$ compared to PiMM subgroups.

The results of the lung function tests in the smoking subgroups are shown in Table 5. The AAT-deficient subgroups had a larger range in FEV_1 and FVC than the control subjects. However, lung function was normal both in ever- and never-smoking PiZ and PiSZ individuals. The PiZ ever- and never-smokers showed a significantly higher mean FVC than PiMM ever- and never-smokers ($p<0.01$), but the FEV_1/FVC ratios did not differ significantly between the groups. No differences were found between ever- and never-smokers within any of the Pi subgroups. No significant differences in lung function were found between the subjects reporting exposure to dust, fumes or gas and those unexposed within any of the Pi subgroups (data not shown).

Sixty-eight PiZ, 32 PiSZ and 84 PiMM subjects performed a reversibility test and of these, three PiZ (4.4%), four PiSZ (13%) and five PiMM (6.0%) had a positive reversibility (n.s.).

A diagnosis of asthma or allergy was reported in 7 of 90 PiZ (7.8%), 5 of 40 PiSZ (11%) individuals and 3 of 84 PiMM subjects (3.6%) (n.s.). Other diagnoses reported in the PiZ and PiSZ individuals were colitis (three PiZ individuals), epilepsy (one PiZ and one PiSZ individual), arthritis (one PiSZ), depression (one PiZ), herniated disc (one PiSZ), headache (one PiSZ), panic anxiety syndrome (one PiSZ), psychosis (one PiZ), rheumatism (one PiSZ) and rosacea (one PiZ).

Drop-outs

Twenty-eight AAT-deficient individuals (15%) did not participate in the survey. Five refused any participation, 18 did not answer letters nor phone calls, three were not registered at a known address, one could not participate due to serious mental illness and one living abroad had no possibility of participating. Three underwent the clinical examination but did not fill in the questionnaire and 25 answered the questions but did not undergo the physical examination or perform spirometry. Their reasons for not seeing their doctor were lack of time or no interest; one expressed fear of detecting disease.

Thirty-seven control subjects (12%) refused all participation and 111 (37%) completed the questionnaire but refused lung function testing in hospital. Lack of time was the most common reason not to participate. Other reasons were no interest, handicap, difficulty in understanding Swedish and moving out of the area. Sixty control subjects (20%) did not answer letters nor phone calls.

Discussion

At 30 years of age these AAT-deficient individuals still have normal lung function. Smoking is less common among the AAT-deficient individuals than the control subjects indicating successful anti-tobacco information to the cohort.

As a whole, the AAT-deficient individuals had more symptoms than the control subjects but the difference was significant only in prevalence of phlegm between the PiSZ and PiMM subjects (Table 2). Among the smokers, the PiZ individuals had significantly higher prevalence of shortness of breath than the PiMM smokers which may indicate that they are more vulnerable to disease (Table 3), dyspnoea on exertion being a classic early symptom of emphysema.[13,14] The PiZ ever-smokers, like the PiMM ever-smokers, also had a significantly increased prevalence of phlegm and wheezing than the never-smokers in the same Pi subgroup. Already at the age of 22 PiZ ever-smokers reported a higher prevalence of wheezing than PiZ never-smokers.[10] No differences were found between the PiSZ and PiMM smokers. The number of smoking PiSZ individuals was small but our results may indicate that PiSZ smokers develop respiratory symptoms later than PiZ smokers. The risk of COPD in individuals with moderate AAT deficiency (PiSZ) is considered lower than in those with severe deficiency (PiZ), but not in any way negligible. In a meta-analysis Dahl et al.[15] showed a three times greater risk for COPD in PiSZ individuals compared to PiMM controls. Another study has shown that PiSZ individuals have a risk of developing emphysema but later than in those with the PiZ phenotype.[5]

Although we found increased prevalence of symptoms in the PiZ and PiMM smokers versus non-smokers, no significant differences in lung function were found between smokers and non-smokers in any Pi group. At 18 years of age, FEV_1/FVC ratio in AAT-deficient adolescents was slightly decreased compared to controls. Ever-smoking AAT-deficient individuals had lower FEV_1 and FEV_1/FVC ratio in comparison with

ever-smoking controls.[6,7] When examined at the ages of 22 and 26, lung function was normal in the PiZ and PiSZ individuals.[8,10] In the present study, at the age of 30, both smokers and non-smokers still have normal lung function when considering sex, age and length and also compared to an age-matched control group drawn from the general population.

A limitation of this study is the fact that the AAT-deficient subjects have been informed about their risk of pulmonary disease and therefore may be more prone to report respiratory symptoms than the control subjects. On the other hand did several controls subjects report respiratory symptoms. Even if the lower lung function values in this group could be due to a systemic measurement failure since all control subjects were examined at the same location, it is more likely that this unintended selection of particularly symptomatic control subjects also have lower lung function, a relation that has been shown in previous studies.[16,17] Another factor that may influence the test results are that the AAT-deficient individuals are used to perform spirometry, thus further contributing to the difference in lung function between AAT-deficient and control individuals.

To our knowledge, this is the only cohort of AAT-deficient young adults that has been followed for as long as 30 years, which is why there are few possibilities to compare with other groups. Results based on data from the Danish AAT Deficiency Registry have shown smoking PiZ individuals older than 25 years, to have a steeper decline in FEV_1 than PiZ non-smokers.[18] Analysis of data from the Swedish AAT registry has shown that never-smoking PiZ individuals have in average normal lung function up to the age of 50.[19] In another study on PiZ individuals included in the Swedish AAT Registry current smokers showed a steeper decline in FEV_1 than ex-smokers and non-smokers.[20] In a general population, the European Community Respiratory Health Survey (ECRHS-I) shows that in individuals between 20 and 44 years of age, smoking causes lower lung function.[21] We did not find such results in AAT-deficient individuals at the age of 30.

A randomised control group from the general population was selected for this study to achieve higher accuracy of the results than at previous checkups. At the 26 year-old checkup the relatively small control group comprised nurses and medical school students, all non-smokers. At the present checkup, a randomly selected group of 300 individuals were drawn from the Swedish population registry. The controls lived in the Skåne County where the University hospital, Malmö, is located. This county is one of the top five Swedish counties regarding prevalence of smoking,[22] which may have contributed to the difference in smoking habits between AAT-deficient individuals and controls.

Difficulty in making contact with the controls postponed their examination and largely explains the small difference in age between AAT-deficient individuals and controls.

In the present study, the participation rate among the AAT-deficient individuals was higher than at the previous checkups. At 26 years of age, 73%the questionnaire and 65% underwent physical examination and spirometry.[8] At 30 years of age, 83% completed the questionnaire and 71% underwent physical examination and spirometry. Becoming a parent increases health concerns and when these AAT-deficient individuals now have their own children they might be more prone to participate. A question frequently asked was how to detect a possible deficiency in their infants.

While the AAT-deficient individuals had a better response frequency than at previous checkups, it was hard to get the controls to participate. This has been reported previously both for the general population in the south of Sweden[23] and for young, smoking men in the north of Sweden.[24] If this is an increasing problem, future surveys will face problems when there are difficulties in recruiting study participants, leading to less accurate results.

In conclusion, at the age of 30 years, AAT-deficient individuals smoke less than age-matched control subjects. The PiZ smokers report higher prevalence of respiratory symptoms which may indicate an early sign of emphysema. All PiZ and SZ individuals still have normal lung function.

Conflict of interest statement

None of the authors has any competing interests, which is hereby confirmed.

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