ORIGINAL ARTICLE

Respiratory symptoms and lung function in young adults with severe α_1-antitrypsin deficiency (PiZZ)

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Background: Neonatal screening for alpha$_1$-antitrypsin (AAT) deficiency was undertaken in Sweden between 1972 and 1974 when 129 infants with severe AAT deficiency (phenotype PiZ) were identified. The cohort has been followed up prospectively.
Methods: 124 PiZ subjects, still alive and still living in Sweden, were invited to a follow up examination at about 22 years of age. The check up included a clinical examination, spirometric tests, and a questionnaire on smoking habits and respiratory symptoms.
Results: Ninety eight subjects (97 PiZZ and 1 PiZ–) subjects attended the follow up. The mean age of the subjects was 22.5 years (range 19.8–24.8). The mean (SD) forced expiratory volume in 1 second (FEV_1) was 98 (14)% predicted, vital capacity (VC) was 103 (14)% predicted, and the mean FEV_1/VC ratio was 83 (7)%. Eighty six subjects had previously undergone spirometric tests. The median follow up time was 4.3 years (range 0.9–7.3). The mean annual change in FEV_1 (% predicted) was –1.2% (95% CI –2.1 to –0.3), in VC (% predicted) was –1.5% (95% CI –2.0 to –0.9), and in the FEV_1/VC ratio (%) was –0.3% (95% CI –0.7 to 0.2). Twenty eight individuals (29%) reported recurrent wheezing. Fifteen subjects (15%) had been diagnosed by a physician as having asthma. Eighteen subjects reported that they had smoked at some time; 10 were current smokers. The mean number of pack years among the ever smokers was 3.4 (range 0.6–10.5). Ten of 18 ever-smokers and 18 of 80 non-smokers reported recurrent wheezing ($p<0.01$), while exertional dyspnoea was reported by six ever smokers and 11 non-smokers ($p<0.05$). Lung function test results did not differ significantly between ever smokers and non-smokers.
Conclusions: Young PiZ adults have essentially normal lung function, but have a high prevalence of asthma symptoms. Smoking in these individuals is associated with an increased frequency of respiratory symptoms.

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Individuals with homozygous PiZZ alpha$_1$-antitrypsin (AAT) deficiency have a considerably increased risk of developing emphysema, especially if they smoke.[1 2] AAT deficiency is also a genetic cause of liver disease in childhood and late adulthood.[3 4] The development of emphysema is mainly due to the decreased amount of AAT in the lung tissue, giving an inadequate inhibition of neutrophil elastase.[5] There is a large variability in the development of lung disease among individuals with severe AAT deficiency which is not fully explained by known environmental and genetic factors.[6]

Neonatal screening for AAT deficiency was undertaken in Sweden between 1972 and 1974 to study the pathophysiology and natural history of lung and liver disease in AAT deficiency. Of 200 000 newborn infants, 127 PiZZ, two PiZ–, 54 PiSZ, and one PiS– individuals were identified.[3] The cohort has been followed up prospectively and clinical data are available since early childhood. Five PiZZ and one PiSZ infants died in early life.[7] From the age of 16 years the check ups have included lung function tests.[8 9]

We report the results of lung function tests, the prevalence of self-reported smoking habits and respiratory symptoms, and physician reported diagnoses in the PiZZ individuals at the 22 year follow up examination.

METHODS

Study population

AAT-deficient individuals identified in the neonatal screening study are invited to follow up studies every fourth year. 122 PiZZ and two PiZ– subjects who were still alive and living in Sweden were invited to the follow up study at about 22 years of age. The check up was performed by a chest physician at the local hospital. Data on the subjects' clinical history were drawn from the earlier check ups.[7 8]

Questionnaire

In connection with the clinical check up the physician filled in a questionnaire regarding diagnoses and results of spirometric tests and liver function tests. The liver function tests included serum aspartate amino transferase (s-ASAT), serum alanine amino transferase (s-ALAT), serum alkaline phosphatase (s-ALP), and gamma glutamyl transferase (s-GT), and were analysed at the local hospitals. The patient filled in a questionnaire which was a modified version of the adult respiratory disease questionnaire used in epidemiological research[10] and identical to that used in the Swedish AAT deficiency register.[11] The results of the following questions were analysed: (1) smoking habits (whether the patient has ever smoked regularly; age at starting, age at stopping, and mean daily consumption of cigarettes); (2) current phlegm (whether the patient usually coughs up phlegm); (3) recurrent wheezing (brought on by damp weather, strong odours, cold (upper respiratory tract infection), or any other circumstances); and (4) exertional dyspnoea (shortness of breath when walking 100 metres on the level).

Lung function tests

Standard spirometric tests were performed at either the respiratory department or the physiological laboratory of the local hospital. Forced expiratory flow in 1 second (FEV_1) and vital capacity (VC) were expressed as a percentage of predicted values according to reference values published by Knudson and coworkers.[12] The FEV_1/VC ratio was expressed as a percentage. Prebronchodilator values for FEV_1 and VC were

Table 1 Prevalence of respiratory symptoms in 80 non-smokers and 18 ever-smokers (ex-smokers and current smokers) at the 22 year check up

	Non-smokers		Ever smokers	
	Yes/total	%	Yes/total	%
Current phlegm	11/78	14%	4/18	22%
Recurrent wheezing	18/80	23%	10/18	56%†
Exertional dyspnoea	11/80	14%	6/18	33%*

*p<0.05; †p<0.01 (χ^2 test).

Table 2 Mean age and lung function in 80 non-smokers and 18 ever smokers (ex-smokers and current smokers) at the 22 year check up

	Non-smokers (n=80)	Ever-smokers (n=18)
FEV_1 (% pred)		
Mean	99	95
95% CI	96–102	88–102
VC (% pred)		
Mean	104	103
95% CI	100–107	96–110
FEV_1/VC (%)		
Mean	84	82
95% CI	82–85	78–85

FEV_1=forced expiratory volume in 1 second; VC=vital capacity.

analysed because reversibility tests were not consistently performed. For individuals participating in a reversibility test, a positive bronchodilator response after inhalation of a β_2 agonist was defined as an increase of ≥12% in FEV_1, a definition used in the previous check ups.[8 9] In the longitudinal analysis of lung function, spirometric results were obtained primarily from the check ups at 18 years of age.[9] In the subjects who did not attend the check up at 18 years of age, lung function was compared with the check up at 16 years.[8]

Statistical analysis

The Student's *t* test was used to compare continuous variables between the groups. Two tailed paired *t* tests were used in the analysis of dependent variables. The χ^2 test was used to compare categorical variables. p values of <0.05 were considered significant.

RESULTS

Lung function, respiratory symptoms, and diagnoses

Of 124 AAT-deficient individuals (122 PiZZ and two PiZ–), 52 men and 46 women participated in the study (97 PiZZ and one PiZ–). The mean age of the study participants was 22.5 years (range 19.8–24.8). The mean (SD) FEV_1 was 98 (14)% predicted (range 52–131), mean VC was 103 (14)% predicted (range 74–142), and the mean FEV_1/VC ratio was 83 (7)% (range 63–99). A reversibility test with inhaled β_2 agonist was performed in 71 subjects, six of whom (8%) had an increase of ≥12% in FEV_1.

Recurrent wheezing was reported by 28 individuals (29%). Fourteen reported wheezing that was brought on by damp weather, 18 suffered from wheezing brought on by cold, five by strong odours, and six suffered from wheezing in other circumstances. Current phlegm was reported by 15 individuals (16%) and exertional dyspnoea by 17 (17%). Eight subjects (8%) reported both current phlegm and dyspnoea.

Fifteen subjects (15%) had been diagnosed by a physician as suffering from asthma. Five of them were being treated with β_2 agonists, two with inhaled corticosteroids, and eight subjects were treated with both. One subject with a diagnosis of asthma received no treatment. Seven subjects (7%) had allergic rhinoconjunctivitis. Other diagnoses reported (one case of each) were rheumatoid arthritis, migraine, epilepsy, moderate congenital cerebral palsy, and endometriosis. No clinical symptoms of liver disease were reported.

The PiZ– subject was a woman aged 23.1 years who had never smoked. She reported no respiratory symptoms but she had a physician-reported diagnosis of rhinoconjunctivitis. The results of her lung function test were as follows: FEV_1 4.3 l (108% predicted), VC 5.5 l (126% predicted), and FEV_1/VC ratio 78%.

Respiratory symptoms and lung function in relation to smoking habits

Ten subjects (three men) were current smokers. Two men and six women reported that they had stopped smoking. Among the ever smokers—that is, ex-smokers and current smokers—the mean number of pack years was 3.4 (range 0.6–10.5). The prevalences of self-reported recurrent wheezing (p<0.01) and exertional dyspnoea (p<0.05) were significantly higher in the ever smokers than in the non-smokers (table 1). Three of 18 ever smokers (17%) and five of 78 non-smokers (6%) reported both current phlegm and exertional dyspnoea. No significant differences in lung function were found between ever smokers and non-smokers (table 2), or between current smokers and non-smokers (data not shown).

Longitudinal analysis of lung function

Eighty six of the 98 participants (46 men) had performed lung function tests previously: 74 subjects at the 18 years check up and 12subjects at the 16 years check up. The mean age of the subjects at time of the first spirometric test was 18.1 years (range 16.0–19.8). The median follow up time was 4.3 years (range 0.9–7.3). The results of the lung function tests at both check ups are shown in table 3. The changes in FEV_1 and VC, expressed as % predicted values, showed a significant annual decline. Fifteen of the 86 subjects reported having smoked at some time, and nine were current smokers at the present check up. The mean annual change in FEV_1, VC, and FEV_1/VC ratio did not differ significantly between ever smokers and non-smokers.

Subjects not participating in the present follow up examination ("drop outs")

Of the 124 PiZ individuals who had been invited to the present follow up, 26 did not attend the clinical examination or spirometric test. Fourteen had attended a previous check up at 16 or 18 years of age and reported that they had never smoked. No information was available on smoking habits or health status of the remaining 13 subjects who had not attended the previous check ups at 16 or 18 years of age.

DISCUSSION

This study was included in the long term follow up of the PiZ individuals identified by the Swedish neonatal AAT screening study during 1972–4. Our results indicate that lung function is still essentially normal in 20–24 year old individuals with severe AAT deficiency (PiZZ). However, all lung function test results, when expressed as a percentage of reference values, were significantly lower than at the previous check up at 16 or 18 years of age (table 3). We compared spirometric results with reference values published by Knudson and coworkers,[12] which we also used in our previous analysis of lung function in the cohort.[13] Using the same reference values in both studies made possible a longitudinal analysis of lung function expressed as percentage predicted values. Overall changes in lung function were small, which may indicate that lung function in these subjects had reached a plateau phase during the observation period.[14]

Table 3 Lung function test results at 16–18 and at 22 years of age and annual change in lung function in 86 subjects who had performed two spirometric tests

	16–18 years (n=86)	22 years (n=86)	Annual change	p (annual change)
FEV_1 (l)				
Mean	4.1	4.2	0.01	NS
95% CI	3.9 to 4.3	4.0 to 4.4	–0.01 to 0.03	
FEV_1 (% pred)				
Mean	105	98‡	–1.2	<0.01
95% CI	101 to 108	95 to 101	–2.1 to –0.3	
VC (l)				
Mean	4.8	5.0†	0.03	<0.001
95% CI	4.6 to 5.1	4.8 to 5.3	0.01 to 0.06	
VC (% pred)				
Mean	109	103‡	–1.5	<0.001
95% CI	106 to 112	100 to 106	–2.0 to –0.9	
FEV_1/VC (%)				
Mean	85	84*	–0.3	NS
95% CI	84 to 87	82 to 85	–0.7 to 0.2	

FEV_1=forced expiratory volume in 1 second; VC=vital capacity.
*p<0.05, †p<0.01, ‡p<0.001 *v* 16–18 years (two tailed *t* test).

In contrast to the results of our previous analysis of risk factors for lung disease in AAT-deficient adolescents,[13] we did not find significant differences in lung function between smokers and non-smokers (table 2). The significantly increased prevalence of self-reported respiratory symptoms in the smoking subjects indicates, however, that harmful effects of smoking are already in progress (table 1). We found similar results at the previous check up at the age of 16–18 years when the presence of current phlegm was more common among ever smokers than non-smokers.[13] All data on smoking history were self-reported by the study participants, and no objective tests were performed to verify their smoking status.

At the 16 year check up the prevalence of self-reported recurrent wheezing among 103 PiZZ individuals was 10.7%.[8] At the present examination 29% of the individuals reported recurrent wheezing, while 15% had physician reported asthma. Previously published reports have suggested that symptoms and diagnosis of asthma are over-represented in severe AAT deficiency.[15] The prevalence of asthma reported in the Swedish general population varies from 5% to 11%.[16 17] Taking into account the high prevalence of self-reported recurrent wheezing in our study, it may support an over-representation of asthmatic symptoms in severe AAT deficiency. It is therefore possible that respiratory symptoms are initially interpreted as "usual" asthma when young PiZZ adults seek health care, which may delay the correct diagnosis. This is especially critical for young PiZZ smokers who may develop irreversible obstructive pulmonary disease within a few years if they continue smoking. Our results may support the WHO recommendation that all adults and adolescents with asthma should be screened for AAT deficiency.[18] Moreover, a postal survey of AAT-deficient individuals in the USA has shown that the mean delay between the first symptoms and the correct diagnosis of AAT deficiency was 7.2 years, indicating that the symptoms may be misunderstood by doctors.[19]

In contrast to other epidemiological studies on AAT deficiency, our study was not affected by selection bias because the study population represented 79% of all PiZZ individuals born in Sweden between 1972 and 1974. Although this is the largest ongoing epidemiological study of AAT deficiency, the number of subjects in subgroups such as smokers is low as a result of effective smoking prevention. The power to detect significant differences between the groups is therefore low and false negative results cannot be excluded. Our results may also have been influenced by the lack of an age and sex matched control group. The follow up of a parallel healthy cohort has not been practically possible because the participants in the study are spread throughout Sweden. We therefore compared the smoking habits of the study participants with the statistics published by Statistics Sweden. In our study three of 52 men (6%) and seven of 46 women (15%) reported that they were current smokers. According to Statistics Sweden, the proportion of daily smokers was about 12% among men and 20% among women aged 16–24 years in Sweden during the same period as the present study was being performed.[20]

We conclude that young PiZZ adults have essentially normal lung function. The prevalence of asthmatic symptoms seems to be high, and smoking is associated with an increased frequency of respiratory symptoms.

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