

Clinical features and prognosis of life time non-smokers with severe α_1 -antitrypsin deficiency

Niels Seersholm, Axel Kok-Jensen

Abstract

Background—The hereditary disorder α_1 -antitrypsin deficiency is characterised by development of severe emphysema at an early age with smoking being the most significant additional risk factor. The purpose of the present paper was to analyse potential risk factors other than smoking for emphysema and to estimate the prognosis of life time non-smokers.

Methods—Patients were identified through the files of the Danish α_1 -antitrypsin deficiency register which contains information on more than 700 persons with the condition. Many of the patients, the non-index cases, were identified from family studies.

Results—There were 75 life time non-smokers with PiZ (27 index cases and 48 non-index cases) aged 20 years or more at entry. Twenty one subjects died during the follow up period. The Standardised Mortality Ratio (SMR) was 3.0 (95% confidence intervals (CI) 1.9 to 4.6). There was no significant difference in SMR between males and females. The SMR was 8.8 (95% CI 5.0 to 14) for the index cases and 0.96 (95% CI 0.3 to 2.3) for the non-index cases based on five deaths. The overall mean % predicted forced expiratory volume in one second (FEV₁) at entry was 83% with a significant difference between index cases (54%) and non-index cases (100%) ($p < 0.001$). The difference in the ratio of FEV₁ to forced vital capacity (FVC) was also highly significant with values of 0.57 and 0.79 for index and non-index cases, respectively ($p < 0.001$). In the non-index group only three had an FEV₁% predicted of less than 70%.

Conclusions—Occupational exposure to airway irritants did not have any significant influence on the development of emphysema. Only a few life time non-smokers develop severe emphysema; most never develop pulmonary symptoms and thus remain undetected unless family members of index cases are screened.

(Thorax 1998;53:265-268)

Keywords: α_1 -antitrypsin deficiency; smoking; mortality; lung function; prognosis

Severe hereditary α_1 -antitrypsin deficiency is characterised by a reduced serum α_1 -antitrypsin level to about 20% of the normal level. α_1 -antitrypsin inhibits the activity of specific proteolytic enzymes such as trypsin, chymotrypsin, and leucocyte elastase.¹ If not

inactivated by α_1 -antitrypsin leucocyte elastase destroys lung connective tissue, particularly elastin, leading to the development of emphysema.^{2,3}

Cigarette smoking is the most significant risk factor in the development of emphysema in patients with α_1 -antitrypsin deficiency and reduction in lung function usually begins in the third and fourth decade of life, leading to early death.⁴⁻⁶ However, most studies have been based on patients examined because of lung disease (index cases), and the natural history of the condition is still unknown. Studies of non-index cases indicate that some subjects with α_1 -antitrypsin deficiency develop only mild emphysema, and that others never develop respiratory symptoms, particularly life time non-smokers.⁶⁻¹⁰

This is of special interest with regard to recommendations for screening for α_1 -antitrypsin deficiency. The rationale for identifying subjects with α_1 -antitrypsin deficiency through screening is to enable the subjects to avoid exposure to risk factors, particularly smoking, which has been successful in a Swedish screening programme where only 3% of adolescents with α_1 -antitrypsin deficiency had taken up smoking.¹¹ The neonatal screening programme in Sweden was discontinued because it created anxiety in parents. However, a subsequent in depth analysis of the psychosocial consequences for the families revealed a generally favourable attitude towards screening.¹²

The aim of the present study of life time non-smokers with α_1 -antitrypsin deficiency was to analyse additional risk factors for emphysema, and to estimate the degree of respiratory symptoms and prognosis with particular emphasis on the large number of non-index cases.

Methods

Patients were identified from the files of the Danish α_1 -antitrypsin deficiency register. Since 1978 patients with α_1 -antitrypsin deficiency have been registered by physicians throughout Denmark. Once a patient is registered a family record is obtained and members at risk of having a Z gene are offered an examination of their Pi type. In this way a large number of family members who do not necessarily have respiratory symptoms have been identified—the non-index cases.

Determination of α_1 -antitrypsin Pi type was usually verified by the Department of Clinical Chemistry at Bispebjerg Hospital by isoelectric focusing as described by Fagerhol and Cox.¹³ If phenotyping had not been performed, the patients were assumed to have genotype PiZZ or PiZ0 if their α_1 -antitrypsin serum level was less than 12 $\mu\text{mol/l}$.

Respiratory Clinic,
Rigshospitalet,
Copenhagen, Denmark
N Seersholm
A Kok-Jensen

Correspondence to:
Dr N Seersholm, Munkelø
12, DK-2860 Søborg,
Denmark.

Received 6 August 1997
Returned to authors
18 September 1997
Revised version received
20 November 1997
Accepted for publication
12 December 1997

In the register smoking status is defined as follows. A smoker is a person who has smoked at least 20 packs of cigarettes or at least one cigarette per day for at least one year in a life time,¹⁴ an ex-smoker is a person who has abstained from smoking for at least three months, and a never smoker is a person who is not a smoker or an ex-smoker.

Data on respiratory symptoms were obtained from a Danish translation of the BMRC questionnaire¹⁵ submitted to all patients alive in August 1991 and consecutively on registration.

For the index cases lung function measurements (spirometry) were reported by the referring physician. When the non-index cases were identified they were encouraged to contact their general practitioner for measurement of lung function. Measurements were performed in accordance with European recommendations.¹⁶ Predicted values of forced expiratory volume in one second (FEV₁) were calculated according to European reference tables.¹⁶ For this study the first spirometric measurement after the patient entered the register was used.

Information on date of death or emigration was obtained from the Danish Central Population Register which was established in 1968 and holds information on all Danish citizens. Death certificates providing information on cause of death were obtained from the Danish National Board of Health.

Patients eligible for the present study were life time non-smokers identified as phenotype Z or with a serum α_1 -antitrypsin level of less than 12 $\mu\text{mol/l}$ who were aged over 20 years at entry to the register.

STATISTICAL ANALYSIS

The period of follow up for survival calculation was taken from the date of entry into the register to the date of death, emigration, or 31 December 1996, whichever came first.⁴ Age, date, and sex specific standardised mortality rates (SMR) were calculated from the Danish reference tables published every year.¹⁷ The *t* test was used to evaluate differences in age, FEV₁, and follow up time and dichotomous variables were evaluated by Fisher's exact test.

Results

The register contained 75 subjects with a PiZ genotype who had never smoked and were 20 years or older at entry. Twenty seven were index cases and 48 were non-index cases (table 1). There were 39% men in the study population with 44% in the index group and 35% in the non-index group (*p* = 0.44). The mean follow up time was 8.7 years (range 3 months to 19 years), 5.4 years (3 months to 16.6 years) for the index cases and 10.6 years (1.2–19 years) for the non-index cases (*p*<0.001). The overall mean age at entry was 50.0 years (range 21.4–85.1 years). The index cases were significantly older at entry than the non-index cases with mean ages at entry of 56.2 (range 27.2–82.6) years and 46.5 (range 21.4–85.1) years, respectively (*p*<0.01). The overall mean serum α_1 -antitrypsin level was

Table 1 Mean (SD) demographic data of the study population

| | Index cases | Non-index cases |
|---|-------------|-----------------|
| No. | 27 (36%) | 48 (64%) |
| Deaths | 16 (59%) | 5 (8.3%) |
| M/F | 12/15 | 17/31 |
| Age at diagnosis (years) | 56.2 (12.7) | 46.5 (13.9) |
| Follow up (years) | 5.4 (3.9) | 10.6 (5.8) |
| α_1 -antitrypsin ($\mu\text{mol/l}$) | 8.2 (3.0) | 8.1 (2.8) |

8.5 $\mu\text{mol/l}$ with no significant difference between the index and the non-index groups.

During the follow up period 21 subjects died, 16 in the index group and five in the non-index group. The median age at death was 66.9 years. The index cases were significantly younger than the non-index cases with median ages at death of 66.5 and 71.1 years, respectively. In table 2 the cause of death, sex, and age at death are shown; most of the index cases died of pulmonary emphysema whereas only one of the non-index cases died of this disease. The SMR for the whole study population was 3.0 (95% confidence intervals (CI) 1.9 to 4.6). There was no significant difference in SMR between men and women with values of 3.4 (95% CI 1.1 to 7.8) and 2.9 (95% CI 1.7 to 4.7), respectively. The SMR was 8.8 (95% CI 5.0 to 14) for the index cases and 0.96 (95% CI 0.3 to 2.3) for the non-index cases.

Spirometric data were missing for eight non-index cases but these did not differ significantly in age at entry, follow up time, or sex from the cases for whom spirometric data were available, although they tended to be older at entry. The initial FEV₁% predicted and FEV₁/FVC ratio for index cases and non-index cases stratified for age at entry are shown in table 3. The overall mean FEV₁% predicted was 83% with a significant difference between index cases (54%) and non-index cases (100%; *p*<0.001). The difference in the FEV₁/FVC ratio was also highly significant with values of 0.57 and 0.79 for index cases and non-index cases, respectively (*p*<0.001). In the index group FEV₁% predicted for the subjects under

Table 2 Cause of death by mode of ascertainment

| Sex | Age at death | Cause of death |
|-----------|--------------|------------------------------------|
| Index | | |
| F | 72 | Unknown |
| F | 77 | Ischaemic heart disease |
| M | 50 | Pulmonary emphysema |
| F | 50 | Pulmonary emphysema |
| M | 56 | Pulmonary emphysema |
| M | 58 | Pulmonary emphysema |
| M | 62 | Pulmonary emphysema/diverticulitis |
| M | 65 | Pulmonary emphysema |
| F | 65 | Pulmonary emphysema |
| F | 66 | Pulmonary emphysema |
| F | 66 | Pulmonary emphysema |
| F | 68 | Pulmonary emphysema |
| F | 71 | Pulmonary emphysema/pneumothorax |
| F | 75 | Pulmonary emphysema |
| F | 79 | Pulmonary emphysema |
| F | 83 | Pulmonary embolism |
| Non-index | | |
| F | 53 | Lung cancer |
| F | 66 | Intra-abdominal cancer |
| F | 71 | Intra-abdominal bleeding |
| F | 74 | Pulmonary emphysema/pneumonia |
| F | 89 | Congestive heart failure |

Table 3 Mean (SD) FEV₁% predicted and FEV₁/FVC of index and non-index cases stratified by age at entry

| | Index cases | Non-index cases | <i>p</i> value (<i>t</i> test) |
|---|-------------|-----------------|------------------------------------|
| All age groups | n = 27 | n = 40 | |
| FEV ₁ % predicted | 54 (25) | 100 (21) | <0.001 |
| FEV ₁ /FVC | 0.57 (0.18) | 0.79 (0.13) | <0.001 |
| N (%) with FEV ₁ % pred ≤70% | 20 (74%) | 3 (8%) | <0.001 |
| Age at entry <50 years | n = 8 | n = 26 | |
| FEV ₁ % predicted | 33 (24) | 98 (18) | <0.001 |
| FEV ₁ /FVC | 0.42 (0.16) | 0.80 (0.12) | <0.001 |
| N (%) with FEV ₁ % pred ≤70% | 4 (50%) | 2 (8%) | <0.001 |
| Age at entry ≥50 years | n = 19 | n = 14 | |
| FEV ₁ % predicted | 47 (19) | 97 (23) | <0.001 |
| FEV ₁ /FVC | 0.58 (0.19) | 0.78 (0.14) | <0.001 |
| N (%) with FEV ₁ % pred ≤70% | 16 (84%) | 1 (7%) | <0.001 |

Table 4 Respiratory symptoms as responded to the BMRC questionnaire

| | Percentage of affirmative responses | | <i>p</i> value (Fisher's exact test) |
|--|-------------------------------------|-----------------------------|---|
| | Index cases (n = 17) | Non-index cases (n = 44) | |
| Cough | 53% | 12% | 0.002 |
| Cough for three consecutive months per year | 47% | 14% | 0.01 |
| Phlegm | 41% | 11% | 0.03 |
| Phlegm for three consecutive months per year | 35% | 11% | 0.06 |
| Shortness of breath | 88% | 46% | 0.003 |
| Attacks of wheeziness | 59% | 27% | 0.04 |
| Asthma | 35% | 9% | 0.02 |
| Pneumonia | 82% | 34% | 0.001 |

50 years at entry was 33% compared with 47% for the subjects over 50 years, but this difference was not significant. In the non-index group only three subjects had FEV₁% predicted under 70% and the oldest person with normal lung function was 67 years, which was also the age of the oldest non-index subject for whom spirometric data were available.

The pulmonary symptoms obtained from answers to the questionnaire for index and non-index cases are shown separately in table 4. Of the 64 eligible subjects (alive in 1991 or later when the questionnaire was submitted), 61 (95%) returned the questionnaire including 17 (94%) index cases and 44 (96%) non-index cases. The index cases had significantly more respiratory symptoms in terms of cough, phlegm, and shortness of breath than the non-index cases. However, of the non-index cases 46% suffered from shortness of breath when hurrying on the level or walking up a slight hill and 27% complained of wheeziness. To the question "have you ever had asthma?" 35% of the index cases and 9% of the non-index cases answered yes (*p*<0.05). When asked whether they had pneumonia 82% in the index group and 34% in the non-index group responded affirmatively (*p*<0.01).

To questions on occupational exposure to dust or chemical agents 35% of the index cases and 30% of the non-index cases answered yes to exposure to dust (*p* = 0.8), and 24% and 14%, respectively, answered yes to exposure to chemical agents or irritants (*p* = 0.4).

Discussion

In studies of the natural history of α_1 -antitrypsin deficiency ascertainment bias has been a major problem. Subjects with severe respiratory symptoms who are mainly smokers

have therefore had a better chance of being included in epidemiological studies, resulting in too pessimistic a prognosis. With the inclusion of more non-index cases in epidemiological studies the variability of lung function impairment and mortality have been recognised, and in previous studies of never smoking non-index cases we found a life expectancy no different from that of the normal Danish population⁶ and an estimated annual decline in FEV₁ of 36 ml/year which is within normal limits.¹⁰

Studies of life time non-smokers with α_1 -antitrypsin deficiency are sparse and comprise mostly index cases.^{2-6,9} The present study of never smokers includes a large proportion of non-index cases found through family studies. We found that the non-index cases did not have increased mortality and very few of them had impaired lung function. The index cases had a tenfold increase in mortality, critically reduced lung function, and severe respiratory symptoms.

Alpha₁-antitrypsin deficiency is a good example of the impact of environmental factors on the phenotype of a genetic disease. However, in the present study the environmental factor, smoking—which is the strongest risk factor for emphysema described so far—was absent. However, some of the subjects had developed severe emphysema. These patients may have been exposed to other factors that contribute to the development of emphysema—for example, other environmental factors such as passive smoking or occupational exposure to dust and chemical fumes, potential predisposing diseases such as asthma or respiratory infections, or other genetic factors.

We did not find any significantly increased exposure to dust and fumes among the index cases. This finding is based on only a few subjects, and even if there was a significant difference it could be due to recall bias. Unfortunately we have no information on the exposure to passive smoking, nor has it been possible to assess whether the index cases were more exposed to environmental pollution. One other study failed to show any association between exposure to dust, chemical fumes, and passive smoking,⁷ but in a recent study of never smokers with α_1 -antitrypsin deficiency it was suggested that occupational exposure to airway irritants was an independent additional risk factor.¹⁸

Significantly more index cases than non-index cases responded affirmatively to the questions concerning asthma and wheeziness. This has also been found by other authors^{4,7,18,19} and the question is whether symptoms are part of emphysema or whether asthma is present together with emphysema in subjects with α_1 -antitrypsin deficiency. It is well known that emphysema in PiZ subjects may be misinterpreted by doctors and patients as asthma before the PiZ diagnosis is established²⁰ and therefore the patient will answer affirmatively to the question on asthma. Several studies have shown that there is an increased number of neutrophils in the bronchoalveolar

lavage fluid from asthma patients, and these neutrophils may result in lung tissue damage and development of emphysema in patients with α_1 -antitrypsin deficiency. With our present knowledge it is impossible to assess whether the symptoms of asthma are part of emphysema or whether asthma causes emphysema in patients with α_1 -antitrypsin deficiency.

A significantly larger proportion of the index cases answered positively to the question of pneumonia, indicating that respiratory infections may contribute to the development of emphysema. However, there is also the dilemma of whether pneumonia develops more often in patients with advanced emphysema or whether frequent attacks of pneumonia result in emphysema in patients with α_1 -antitrypsin deficiency. There is no doubt that patients with severe emphysema or chronic obstructive pulmonary disease (COPD) often have pneumonia and we think this is the reason for the higher proportion of affirmative responses among the index cases. However, it has been suggested that childhood respiratory infections lead to the development of COPD.²¹ A prospective study of 103 Swedish children with α_1 -antitrypsin deficiency showed that they had normal lung function when they reached adulthood, indicating that childhood respiratory infections are not a major factor for emphysema.²²

Can other genetic factors contribute to the development of respiratory disease in these subjects? Silverman and colleagues have done extensive work on this matter and have suggested that there might be other genetic factors involved, but their studies were limited by a small number of families.^{23, 24} It would be interesting to compare the lung function of the parents of index cases with that of the parents of non-index cases. Unfortunately only a few of the parents have undergone spirometric testing and such a comparison was not possible. From our data we are not able to determine whether environmental factors or other genetic factors are responsible for the advanced emphysema among the index cases.

It is important to emphasise that the non-index cases did not have an excess mortality and had, on average, normal lung function, and most never smokers with α_1 -antitrypsin deficiency live a normal life without respiratory symptoms.

In view of the good prognosis of never smokers, insurance companies should reconsider their policy and not deny life insurance to life time non-smokers with α_1 -antitrypsin deficiency identified through screening. Furthermore, it is important to identify α_1 -antitrypsin deficiency homozygotes early with regard to counselling to avoid smoking and, although the evidence for other environmental factors in the development of emphysema is weak, exposure to high degree of airway irritants should be avoided. We will encourage screening of family

members of index cases and, depending on the frequency of the Z gene in the population, it might be worthwhile to screen all adults at the age of 15–20 years which is the age at which people usually start smoking. Once identified, individuals with α_1 -antitrypsin deficiency should be followed with spirometric testing every 3–5 years in order to detect those with an accelerated decline in lung function.

- 1 Brantly M, Nukiwa T, Crystal RG. Molecular basis of alpha-1-antitrypsin deficiency. *Am J Med* 1988;84:13–31.
- 2 Eriksson S. Studies in alpha 1-antitrypsin deficiency. *Acta Med Scand* 1965;S432:1–85.
- 3 Tobin MJ, Cook PJ, Hutchison DC. Alpha 1-antitrypsin deficiency: the clinical and physiological features of pulmonary emphysema in subjects homozygous for Pi type Z. A survey by the British Thoracic Association. *Br J Dis Chest* 1983;77:14–27.
- 4 Larsson C. Natural history and life expectancy in severe alpha 1-antitrypsin deficiency, PiZ. *Acta Med Scand* 1978;204:345–51.
- 5 Janus ED, Phillips NT, Carrell RW. Smoking, lung function, and alpha 1-antitrypsin deficiency. *Lancet* 1985;ii:152–4.
- 6 Seersholm N, Kok-Jensen A, Dirksen A. Survival of patients with severe alpha 1-antitrypsin deficiency with special reference to non-index cases. *Thorax* 1994;49:695–8.
- 7 Silverman EK, Pierce JA, Province MA, et al. Variability of pulmonary function in alpha-1-antitrypsin deficiency: clinical correlates. *Ann Intern Med* 1989;111:982–91.
- 8 Poller W, Faber JP, Olek K. Highly variable clinical course in severe alpha 1-antitrypsin deficiency: use of polymerase chain reaction for the detection of rare deficiency alleles. *Klin Wochenschr* 1990;68:857–63.
- 9 Black LF, Kueppers F. Alpha-1-antitrypsin deficiency in nonsmokers. *Am Rev Respir Dis* 1978;117:421–8.
- 10 Seersholm N, Kok-Jensen A, Dirksen A. Decline in FEV₁ among patients with severe hereditary alpha-1-antitrypsin deficiency type PiZ. *Am J Respir Crit Care Med* 1995;152:1922–5.
- 11 Sveger T, Thelin T, McNeil TF. Young adults with alpha-1-antitrypsin deficiency identified neonatally: their health, knowledge about and adaptation to the high-risk condition. *Acta Paediatr* 1997;86:37–40.
- 12 McNeil TF, Sveger T, Thelin T. Psychosocial effects of screening for somatic risk: the Swedish alpha-1-antitrypsin experience. *Thorax* 1988;43:505–7.
- 13 Fagerhol MK, Cox DW. The Pi polymorphism. Genetic, biochemical and clinical aspects of human alpha 1-antitrypsin. *Adv Human Genet* 1981;11:1–62.
- 14 American Thoracic Society. Statement by the Committee on Standards for Epidemiology Surveys on Chronic Respiratory Disease of the American Thoracic Society. New York: National Tuberculosis and Respiratory Disease Association. 1969;32.
- 15 Medical Research Council Committee on the Aetiology of Chronic Bronchitis. Standardized questionnaires on respiratory symptoms. *BMJ* 1960;2:1665.
- 16 Quanjer PH. Standardized lung function testing. *Eur Respir J* 1993;6(Suppl 16):3–102.
- 17 Danmarks Statistik (National Danish Statistics Bureau). *Statistical yearbook*. 1990: 94.
- 18 Piitulainen E, Tornling G, Eriksson S. Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with α_1 -antitrypsin deficiency (PiZZ). *Thorax* 1997;52:244–8.
- 19 Brantly ML, Paul LD, Miller BH, et al. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis* 1988;138:327–36.
- 20 Stoller JK, Smith P, Yang P, et al. Physical and social impact of alpha 1-antitrypsin deficiency: results of a survey. *Cleve Clin J Med* 1994;61:461–7.
- 21 Burrows B, Knudson RJ, Lebowitz MD. The relationship of childhood respiratory illness to adult obstructive airway disease. *Am Rev Respir Dis* 1977;115:751–60.
- 22 Sveger T, Piitulainen E, Arborelius M Jr. Clinical features and lung function in 18-year-old adolescents with alpha 1-antitrypsin deficiency. *Acta Paediatr* 1995;84:815–6.
- 23 Silverman EK, Province MA, Campbell EJ, et al. Biochemical intermediates in alpha 1-antitrypsin deficiency: residual family resemblance for total alpha 1-antitrypsin, oxidized alpha 1-antitrypsin, and immunoglobulin E after adjustment for the effect of the Pi locus. *Genet Epidemiol* 1990;7:137–49.
- 24 Silverman EK, Province MA, Campbell EJ, et al. Family study of alpha 1-antitrypsin deficiency: effects of cigarette smoking, measured genotype, and their interaction on pulmonary function and biochemical traits. *Genet Epidemiol* 1992;9:317–31.