Survival of patients with severe α_1-antitrypsin deficiency with special reference to non-index cases

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Abstract

Background **– Previous estimates of the survival times of patients with α_1-antitrypsin deficiency have been based on selected patients.**

Methods **– The survival times of 397 patients with severe α_1-antitrypsin deficiency identified by pulmonary impairment (index cases) or through family studies (non-index cases) were compared.**

Results **– The overall median survival time was 54·5 years with no significant difference between men and women. Survival for index cases was less than for the non-index cases regardless of smoking history (49·4 years and 69·3 years respectively). When index and non-index cases were analysed separately there was no difference between the survival of smokers and never smokers in the index group. In the non-index group smokers had a shorter survival time than never smokers. The survival time of never smokers was similar to that of the normal Danish population.**

Conclusions **– The prognosis of severe α_1-antitrypsin deficiency is better than previously assumed and, although smoking is a major risk factor, the development of emphysema in patients with severe α_1-antitrypsin deficiency is multifactorial.**

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Alpha$_1$-antitrypsin exists in over 70 biochemical genetic variants – the protease inhibitor system (Pi).[1] Epidemiologically the most significant Pi types are M, S, and Z. Homozygotes deficient of the Z type have only 10–20% of the normal serum concentration of the inhibitor and have an increased risk of developing pulmonary emphysema, with cigarette smoking being the most important risk factor.

Most studies of the effect of α_1-antitrypsin deficiency on lung function have shown the development of early emphysema, but the patients in these studies were highly selected. A few studies have compared severely disabled PiZ patients with their relatives and found a wide range of lung function impairment, suggesting that factors other than cigarette smoking contribute to emphysema and early death.[2–4]

Calculation of survival time in patients homozygous for type PiZ indicates that they have a poor prognosis, but such estimates are based on hospital populations already suffering from respiratory symptoms at the time of diagnosis.[5] Calculations based on population frequencies of the Z gene suggest that about 90% of these subjects are not accounted for in such surveys.

To calculate the true mortality rate of all type PiZ homozygotic subjects large population screens must be performed and the affected subjects followed through their whole life span – a task that started in Sweden in 1972.[6]

The aim of this study was to estimate the survival time of patients with α_1-antitrypsin deficiency and to compare index cases with non-index cases. By including a large number of non-index cases in the analysis selection bias was reduced.

Methods

Patients were selected from the Danish α_1-antitrypsin deficiency register in Copenhagen. Since 1978 patients have been registered by physicians throughout Denmark, and 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. More than 2500 family members of index cases have been tested, and the register contains 565 persons with severe α_1-antitrypsin deficiency of whom 310 are index cases and 255 are non-index cases.

Determination of α_1-antitrypsin Pi type was usually verified by isoelectric focusing as described by Fagerhol and Cox.[7] If phenotyping had not been performed the patients were assumed to have phenotype PiZ or PiZ0 if their α_1-antitrypsin serum level was less than 12 μmol/l. This value was derived from our data in which serum levels of subjects with known phenotypes PiZ and PiSZ were compared.

Information on date of death or emigration was obtained from the Danish Central Population Register. A smoker was defined as a person who had smoked at least 20 packs of cigarettes or at least one cigarette per day for at least one year in a lifetime.[8]

Patients who were considered eligible for the present study were aged 20 years or more, with a Pi type of ZZ or a serum α_1-antitrypsin level of less than 12 μmol/l, and with known mortality status – that is, dead or alive – at the closing date of the study (1 September 1992).

Of the 565 patients in the register, 36 were under 20 years, 72 were of the phenotype PiSZ, and 11 had a serum α_1-antitrypsin level greater than 12 μmol/l. Smoking history was not available for 49 patients, leaving 397 patients for analysis (284 verified PiZ and 113

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with an α_1-antitrypsin level of less than 12 μmol/l).

DATA ANALYSIS

Cumulative survival probabilities were estimated by the life table method.[9] A survival rate of 100% at 20 years of age was assumed. The period of follow up for survival calculation was taken from the age at which α_1-antitrypsin deficiency was diagnosed, or at age 20 years – whichever was the later – to the date of death, emigration, lung transplantation, or September 1992.[5]

Mortality rates of the subgroups were compared using the log rank test with a significance level of 5%.[10] The χ^2 test was used for comparison of the study groups with the normal Danish population.

The median survival times with 95% confidence intervals were calculated by the method described by Peto *et al.*[10]

Results

The Danish α_1-antitrypsin deficiency registry is nationwide with the number of patients registered ranging from 2·9 per 100 000 in Århus county to 18 per 100 000 in Copenhagen city.

In table 1 the distribution of the age at entry into the register is shown. Assuming a frequency of PiZ of 1/1600,[11] the estimated total number of persons with the phenotype PiZ in Denmark was calculated, as well as the proportion of the total number registered. In the age category 30–59 years, between 20–28% of the estimated number of patients with α_1-antitrypsin deficiency are registered.

Of the 397 subjects entering the study, 112 died during follow up. Thirteen patients received a lung transplant and two emigrated. Median follow up time was 5·6 (range 0–21) years.

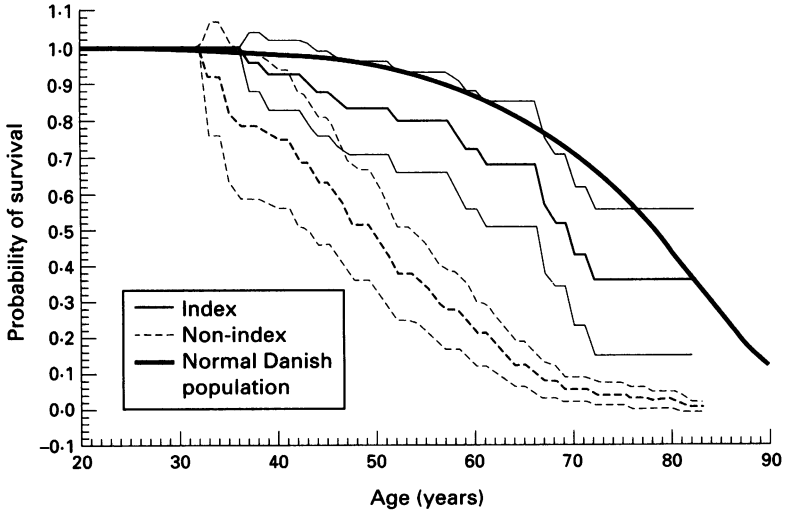

Figure 1 Cumulative probability of the survival time of index cases and non-index cases with 95% confidence intervals. Survival of the normal Danish population is shown for comparison.

The demographic data of the study population are shown in table 2. Men and women are equally represented, and the 252 index cases and 145 non-index cases differed significantly in smoking habits and follow up time. Of the index cases 8% had never smoked compared with 33% of the non-index cases. The non-index cases had been followed for longer than the index cases with a median follow up time of 7·4 years compared with 4·7 years. There was no significant difference in age at diagnosis between the index and non-index cases.

The overall median survival time was 54·2 years (95% confidence limits 50·2 to 58·3), with no significant difference between men and women. Figure 1 summarises the survival curves of index and non-index cases. There was a highly significant difference in survival between the two groups with a median survival of 49·4 years (95% CI 42·4 to 53·6) for the index group and 69·3 years (95% CI 65·9 to 82·1) for the non-index group ($p < 0.0001$), both being significantly less than the survival of the normal Danish population.

The survival of smokers was significantly less than for non-smokers ($p < 0.0001$) with a median survival time of 51·8 years (95% CI 47·2 to 56·1) for smokers and 66·8 years (95% CI 65·3 to 75·1) for never smokers (fig 2). The survival time of the never smokers was significantly less than for the normal Danish population.

To analyse the interaction between mode of identification and smoking history the survival times of smokers and never smokers were compared for index and non-index cases

Table 1 Age distribution of the study population, and observed and estimated number in each group

Age	*Observed number*	*Expected number (1/1600)*	*Observed/expected*
20–29	37	498	0·07
30–39	94	467	0·20
40–49	138	490	0·28
50–59	85	346	0·25
60–69	35	297	0·12
>70	8	284	0·03
Total	397	2382	0·17

Table 2 Demographic data of study population

	Index cases (n=252)	*Non-index cases (n=145)*
M:F	137:115	65:80
Alive	145	125
Dead	94	18
Lost	0	2
Lung transplant	13	0
Smoking history[1]:		
Smokers	231(92%)	97(67%)
Never smokers	21(8%)	48(33%)
Median (range) age at diagnosis (years)	46·3(20–83)	41·9(20–85)
Median (range) follow up time (years)[2]	4·7(0–17)	7·4(1–21)

[1]χ^2 test, $p < 0.001$; [2]Mann-Whitney test, $p < 0.01$.

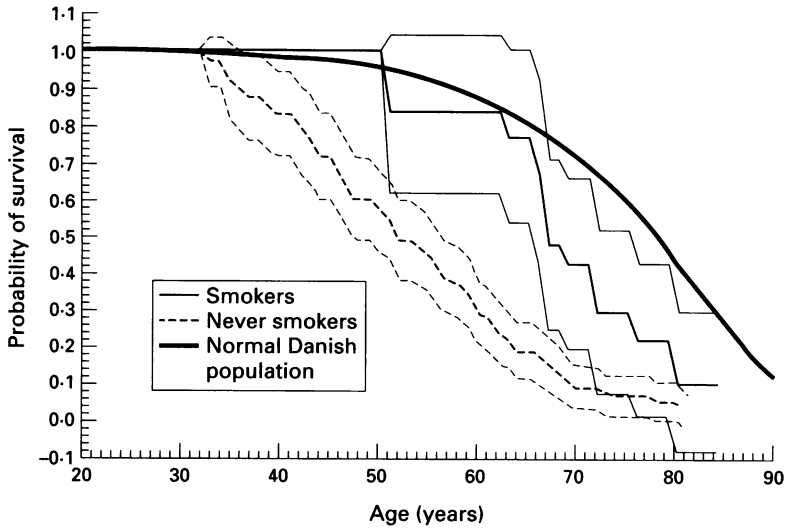

Figure 2 Cumulative probability of the survival time of smokers and non-smokers with 95% confidence intervals. Survival of the normal Danish population is shown for comparison.

separately (table 3). For index cases the survival time of smokers and never smokers was not significantly different, but for non-index cases the survival of smokers was less than that of never smokers ($p < 0.05$). For non-index cases the survival time of never smokers was not significantly different from that of the normal Danish population.

A quantitative analysis of smoking history was performed using the Cox proportional hazards regression model with time dependent variables.[10] Index cases were analysed against non-index cases, with sex and the total lifetime tobacco consumption in terms of pack-years being entered as covariates. Index cases had a relative risk of 3·47 (95% CI 2·02 to 5·98) compared with non-index cases. Neither sex nor the total tobacco consumption influenced the excess mortality of index cases. When the non-index cases only were analysed the excess mortality of smokers applied to patients with a smoking history of more than 10 pack years with a relative risk of 3·1 (95% CI 1·01 to 9·7).

Discussion

Previous studies on the natural history of α_1-antitrypsin deficiency indicate that it is a serious disorder with considerably reduced life expectancy. Larsson[5] determined the cumulative probability of survival in 248 PiZ subjects and found it significantly reduced compared with the normal Swedish population. The median survival time for smokers was around 40 years. It is important to note that 90% of the subjects in Larsson's study were highly selected and were included in his survey largely because of the development of respiratory impairment.

In studies of index and non-index cases there was significantly less impairment of lung function among the non-index cases than among the index cases.[2-4] Other authors have discussed the variability in the clinical course of α_1-antitrypsin deficiency and have recognised that selection bias could skew the natural history.[2 4 5 12 13]

In the present study the patients with α_1-antitrypsin deficiency were drawn from a register covering all counties of Denmark. A large number of non-index cases were found through extensive family studies, and in the 40–49 year age group 28% of the estimated total number of patients had registered.

This study is not devoid of selection bias because it is possible that in some families with α_1-antitrypsin deficiency even smokers do not develop emphysema and thus will never be diagnosed. Selection bias has been overcome to some extent by comparing the survival of 252 patients with α_1-antitrypsin deficiency identified because of lung disease with 145 identified through family studies. A large difference in life expectancy was found even when we controlled for smoking history. The two groups differed significantly with respect to follow up time and smoking history. The age at diagnosis was higher for the index cases, but not significantly. The differences in age at diagnosis and follow up time have been taken into account in our calculations by using the actuarial life table method and cannot explain the variability in survival.

When the patients were stratified for mode of identification and the survival of smokers and never smokers was analysed, smoking did not seem to be the main risk factor. Among index cases there was no significant difference in survival time between smokers and never smokers; this may be a result of the limited number of never smokers in the study. The total lifetime tobacco consumption in terms of pack years did not influence survival when included in the Cox regression model.

There is no doubt that smoking is a major risk ractor, but other factors must contribute to the development of lung disease and the subsequent reduced survival time. Eriksson and others have suggested that frequent pulmonary infections lead to release of neutrophil elastase causing lung destruction.[14 15] Consequently, the index cases may have had more infections in childhood. It is also possible that passive smoking contributes to the earlier onset of emphysema among the index cases, but we have no data to support this. The reason for the variability in development of impairment of lung function and subsequently reduced survival must be multifactorial, and with our present knowledge a comprehensive explana-

Table 3 Survival time of smokers and never smokers stratified by mode of identification

	Index cases		*Non-index cases*	
	Smokers	*Never smokers*	*Smokers*	*Never smokers*
No.	231	21	97	48
Alive	135	10	83	42
Dead	83	11	14	4
Lost	0	0	0	2
Transplant	13	0	0	0
Median survival (95% CI)	49·1(42·3 to 54·0)	51·1(50·5 to 65·2)	67·0(58·0 to 70·0)	>75*

*The number of never smokers among the non-index cases is too small to calculate 95% confidence intervals.

tion is not possible.

In contrast to previous studies our population contained an equal number of men and women with no sex specific difference in survival rate. The male predominance characteristic of other studies is probably a selection problem caused by the higher proportion of male smokers in the general population.[4 16–18]

In previous studies the life expectancy of patients with α_1-antitrypsin deficiency was estimated to be about 40–50 years. We found an overall median life expectancy of 54·6 years, but with large differences between index and non-index cases. The true life expectancy is probably somewhere in between the two groups and can be estimated more accurately when more non-index cases are included in the calculations and the follow up time is longer.

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