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ORIGINAL RESEARCH

Survival in the Swedish cohort with alpha-1-antitrypsin deficiency, up to the age of 43–45 years

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Background: Alpha-1-antitrypsin deficiency (AATD) is a hereditary disorder. AATD is a known risk factor for the development of emphysema and liver disease. A cohort of severe (PiZZ) and moderate (PiSZ) AAT-deficient newborn infants was identified by the Swedish national neonatal AAT screening in 1972–1974 and has been followed up since birth. Our aim was to study survival in this cohort up to 43–45 years of age in comparison with the general Swedish population.

Methods: Data from 127 PiZZ, 2 PiZnull, 54 PiSZ, and 1 PiSnull subjects, who were identified by the neonatal screening in 1972–1974, were included in the study. To compare death rates in the PiZZ and PiSZ individuals with the general Swedish population, a standardized mortality ratio (SMR) was calculated as the ratio of observed to expected deaths.

Results: Seven PiZZ subjects died during the follow-up, to be compared with an expected 3.66 deaths for the general population, giving an SMR of 1.91 (95% CI 0.77–3.94). Four PiSZ subjects died compared to an expected 1.53 deaths, giving an SMR of 2.61 (95% CI 0.71–6.71). The cumulative probability of survival up to the age of 45 years was 94% (95% CI 90%–98%) for the study population. Six deaths occurred before the age of 8 years.

Conclusion: Up to 43–45 years of age, there was no difference in survival between PiZZ and PiSZ individuals in comparison with the Swedish general population. The majority of deaths occurred during childhood.

Keywords: alpha-1-antitrypsin deficiency, causes of death, screening, survival

Introduction

Severe alpha-1-antitrypsin deficiency (PiZZ) is a risk factor for the development of emphysema and liver disease. The pathogenesis of the lung disease is mainly due to the low level of circulating alpha-1-antitrypsin (AAT) in the plasma and lung tissue. This in turn leads to lack of inhibition of serine proteases such as neutrophil elastase, prolonged and accumulative tissue damage of the lung parenchyma, and development of emphysema. Liver disease is the second most frequent clinical manifestation and typically presents as neonatal cholestasis in infancy, and cirrhosis and hepatocellular carcinoma in late adulthood. Smokers with moderate AAT deficiency (AATD) (PiSZ) have also increased risk for the development of COPD.[1,2]

The early studies of survival in severe AATD have indicated poor prognosis with reduced life expectancy.[3] However, our recently published, register-based studies have shown that PiZZ never-smokers, identified by screening, have similar life expectancy as the general Swedish population.[4,5]

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The Swedish Neonatal AAT screening was performed over a 2-year period, 1972–1874. The aims of the screening were to assess the prevalence of AATD in Sweden and to study its natural course and the pathophysiology of liver and lung diseases. Among 200,000 newborn infants, 127 PiZZ, 2 PiZnull, 54 PiSZ, and 1 PiSnull subjects were identified.[6] This cohort has been followed up regularly, every fourth year in adulthood. Serial reports of prospective follow-ups of the cohort up to the age of 38 years have been published.[7–16] The follow-ups at the ages of 18, 22, 26, and 30 years revealed normal lung and liver function in PiZZ and PiSZ individuals. At the 34-year follow-up, the PiZZ ever-smokers had significantly lower carbon monoxide transfer coefficient (Kco) in comparison to the PiSZ and PiMM never-smokers.[13] At the 37–39-year follow-up, ever-smoking PiZZ individuals have shown physiological changes indicating early signs of emphysema.[16]

The aims of this study were to analyze the mortality and causes of death up to the age of 43–45 years in this cohort of AATD individuals identified by neonatal screening.

Patients and methods

Study population

All 127 PiZZ, 2 PiZnull, 54 PiSZ, and 1 PiSnull subjects who were identified by the neonatal screening in 1972–1974 were included in the study. Ten additional PiZZ subjects who were born abroad during the screening period (1972–1974) were not identified initially by the screening. They were excluded from the analyses. Details of smoking habits were obtained from the questionnaires at the time of check-ups at the age of 30, 34, and 38 years and at the ongoing check-up at the age of 42 years. Smoking status was based on the subject's self-reported smoking habits and was divided into two groups: ever-smokers, including former and current smokers, and never-smokers. A smoker was defined as a subject who had smoked more than one cigarette per day for at least 1 year, or more than 20 packs of cigarettes during his life time.

The follow-up time was from the date of birth to the date of death or study end (February 1, 2018). The date of death was obtained from the Swedish Registry of Deaths. Vital status was known for all 184 individuals at the closing point of the study. For each death, the medical records and if the patient died at home, last outpatient's visits, and the death certificate were reviewed. An autopsy protocol for patients who had undergone complete post-mortem examination was obtained from The Department of Pathology at which the autopsy was performed. The underlying and immediate causes of death were determined based on the medical records and autopsy protocols. The study was conducted in accordance with the Helsinki declaration and was approved by the Regional Ethical Review Board of Lund, Sweden.

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS 22.0) software was employed for the statistical analyses. Cumulative, crude survival probabilities were estimated using life table. A standardized mortality ratio (SMR) was calculated as the ratio of observed to expected deaths in order to compare the death rates in the PiZZ individuals with the general Swedish population. The expected numbers of deaths were obtained using age-, sex-, and date-specific death rates published in Sweden annually (Statistics Sweden). Confidence intervals for the SMR were computed from the Poisson distribution. A P-value of <0.05 was considered significant.

Results

The demographic data of the study population are presented in Table 1. All subjects in the cohort were included in the analyses. None of these subjects had undergone lung or liver transplantation, and none of them received AAT augmentation therapy.

Survival

Five PiZZ children and one PiSZ child died before the age of 8 years. Further, two PiZZ and three PiSZ individuals died during the follow-up (Table 2). The cumulative probability of survival up to the age of 45 years was 94% (95% CI 90%–98%) for the study population as a whole, 93% (95% CI 86%–98%) for the PiSZ group, and 94% (95% CI 90%–98%) for the PiZZ group.

A total of eleven deaths (6%) occurred during the follow-up. Among the PiZZ subjects, seven deaths (5%) occurred during the follow-up compared with the expected 3.66 deaths, which gives an SMR of 1.91 (95% CI 0.77–3.94). Among the PiSZ individuals, four deaths (7%) vs the expected 1.53 deaths occurred, which gives an SMR of 2.61 (95% CI

Table 1 Demographic data of the study population

Characteristics	Total N=184	PiZZ and PiZnull N=129	PiSZ and PiSnull N=55
Men, n (%)	106 (58)	76 (59)	30 (55)
Smoking habits			
Never, n (%)	127 (69)	93 (72)	38 (69)
Former, n (%)	30 (16)	26 (20)	7 (13)
Current, n (%)	11 (6)	5 (4)	6 (11)
Unknown	16 (9)	5 (4)	4 (7)
Deaths, n (%)	11 (6)	7 (5)	4 (7)

Table 2 SMRs of a cohort of severe (PiZZ) and moderate (PiSZ) AAT-deficient newborn infants was identified by neonatal screening

	No	Observed/ expected	SMR (95% CI)
PiZZ and PiZnull	129	7/3.66	1.91 (0.77–3.94)
PiSZ	55	4/1.53	2.61 (0.71–6.71)
Men	106	6/3.52	1.71 (0.63–3.72)
Women	78	5/1.67	3.00 (0.97–7.00)

Abbreviations: AAT, Alpha-1-antitrypsin; SMR, standardized mortality ratio.

0.71–6.71). There was no significant difference in mortality rate between the PiZZ and PiSZ individuals. Gender-specific SMRs were 1.71 (95% CI 0.63–3.72) for men (six deaths vs expected 3.52) and 3.00 (95% CI 0.97–7.00) for women (five deaths vs expected 1.67) (ns) (Table 2). Because six individuals died before 8 years of age, smoking habits could not be included in the mortality analysis.

Causes of death

PiZZ subjects

Before the age of 6 months, 22 (15 boys and seven girls) of the 127 PiZZ and 2 PiZnull children (17%) manifested clinical signs of liver disease. Fourteen of them had severe liver disease (prolonged jaundice) and eight had clinical signs of mild liver disease.

The causes of death are presented in Table 3. Before the age of 8 years, four of the 22 PiZZ children with neonatal liver disease died. Two died of liver failure due to liver cirrhosis. One child with known severe aplastic anemia died of bacterial septicemia. Post-mortem examination revealed early signs of liver cirrhosis. One PiZZ child died because of severe physical trauma after a car accident. Autopsy revealed signs of liver fibrosis. The remaining 18 PiZZ children with liver disease during the neonatal period are alive and none of them have any clinical signs of liver disease been reported. One PiZZ woman died in adulthood. Due to the fact that she was born with hydrocephalus and suffered from severe mental retardation and epilepsy, she had not participated in any of the follow-ups. The cause of death was septicemia due to bacterial pneumonia. One PiZZ man with known alcohol abuse suffered from liver cirrhosis and died because of septicemia and liver failure (Table 3).

PiSZ subjects

None of the 54 PiSZ and the PiSnull individuals had clinical signs of liver disease in childhood. One PiSZ child died of the sudden infant death syndrome. Liver disease was the cause of death in two of three PiSZ subjects who died in adulthood. One of them had known alcohol addiction (Table 3). One of them was a current and one was a former smoker. No deaths related to lung disease were reported.

Discussion

In this only ongoing follow-up of a population-based cohort of PiZZ and PiSZ individuals, identified by a national

Table 3 Characteristics, previous liver disease, and causes of death in eleven deceased individuals

No	Sex	Pi	Smoking habits	Age at death	Liver disease	Cause of death	
						Underlying	Immediate
1	Female	ZZ	–	0.16 years (2 months)	Hepatomegaly, liver cirrhosis	Atrium septum defect, liver cirrhosis	Osteomyelitis, septicemia
2	Male	ZZ	–	3.7 years	Hepatomegaly, liver cirrhosis	Aplastic anemia	Bleeding diathesis
3	Male	ZZ	–	5.6 years	Hepatomegaly, liver fibrosis		Traffic accident
4	Female	ZZ	–	7.1 years	Hepato-splenomegaly	Ascetic liver failure	Coma hepatica
5	Male	ZZ	–	7.7 years	Not known	IgG deficiency	Septicemia
6	Female	ZZ	–	36 years	No	Mild thanatophoric dysplasia	Pneumonia, septicemia
7	Male	ZZ	Former	42 years	Liver cirrhosis	Liver cirrhosis, esophagus varices	Septicemia, liver failure
8	Male	SZ	–	0.28 years (3 months)	Icterus		Sudden infant death syndrome
9	Male	SZ	Former	36 years	Fatty liver at autopsy		Methadone overdose[a]
10	Female	SZ	Current	38 years	Hepatomegaly and fatty liver at autopsy		Acute myocarditis
11	Female	SZ	Current	39 years	Alcohol-induced liver cirrhosis[a]	Liver failure	Septicemia

Note: [a]The patient had drug and alcohol abuse.

neonatal screening, who are followed up since birth, no statistically significant differences in all-cause mortality up to the age of 43–45 years were found in comparison with the Swedish general population. The study was initiated in the 1970s in order to determine the natural course of potential liver and lung disease in AAT deficiency, and to study the possible effects of exogenous and endogenous factors.

The most of the previously published studies of AATD have been influenced by ascertainment bias because the majority of the patients have been identified because of liver or respiratory disease.[3,17] Therefore, the majority of the asymptomatic PiZZ individuals have remained unidentified. The first study on the life expectancy in severe AATD was published by Larsson. The study population was highly selected. He noted that severe AATD is associated with poor prognosis.[3] The cumulative probability of survival was significantly reduced compared with the general Swedish population, and the median survival in PiZZ smokers was only 40 years. In the present study, smoking habits were known in four of the five AAT-deficient subjects who died in adulthood. Despite the fact that two of them were current smokers and two were former smokers, no visual sign of emphysema was reported in the post-mortem examination. Thus, none of the deceased AAT-deficient subjects, up to age of 40 years, has died because of COPD. Furthermore, in the recently terminated follow-up of the cohort at the age of 38 years, no emphysema was found in CT, and no diagnosis of COPD was reported in the AAT-deficient subjects. However, the pulmonary function tests revealed signs of COPD in PiZZ smokers.[16] Thus, the prognosis is better both in smoking and non-smoking PiZZ individuals than the initial analyses have indicated. In another previously published study of 124 PiZZ individuals, Brantly et al found a cumulative probability of 52% for survival up to 50 years of age and only a 16% chance of surviving up to 60 years of age.[17] Our study shows that the PiZZ individuals have a cumulative probability of survival of 94% up to 43–45 years of age. These results are in accordance with our recently published analyses on survival in PiZZ individuals included in the Swedish AAT deficiency register in which we found a similar life expectancy in never-smoking PiZZ individuals as in non-smoking Swedish population.[5] Up to age of 43–45 years, the majority of the deaths in this cohort have occurred in childhood, and liver disease was the main underlying cause of death. Thus, in PiZZ subjects, the risk of severe liver disease is substantial in infancy and in late adulthood.[4,6,18,19]

One PiZZ man, who died in adulthood, had a history of alcohol abuse and suffered from liver cirrhosis. It is possible that PiZZ subjects are more prone to develop alcohol-induced liver disease than those with the PiMM phenotype. None of the two PiZZ subjects in the present study who died in adulthood had shown any clinical signs of liver disease in infancy. The surviving PiZZ subjects with liver disease in the neonatal period have not suffered from liver disease during the follow-up period. Thus, liver disease in childhood does not seem to have a direct influence on the risk of liver disease in young adults.

We did not find any increased mortality risk in PiSZ subjects up to 43–45 years of age in comparison with the Swedish general population. Life expectancy is poorly studied in PiSZ individuals. Green et al have previously compared survival between adult PiZZ, PiSZ, and PiMM individuals, and found that PiSZ patients had better survival than the PiZZ and PiMM patients suffering from COPD.[20] The analysis was based on a cohort of PiZZ and PiSZ subjects included in the UK AATD register. The majority of the patients were identified because of lung disease.

The PiSZ phenotype is not proven as a definite risk for liver disease. None of the PiSZ subjects in this cohort suffered from liver disease in childhood. However, the three PiSZ subjects, who had died in adulthood, had liver steatosis or cirrhosis at post-mortem examination. Two of them had a reported history of alcohol or drug abuse. As in the PiZZ subjects who died because of liver failure, it remains unclear whether their liver cirrhosis was caused by alcohol abuse or was due to the PiSZ phenotype per se, or whether the PiSZ phenotype implies an increased risk of liver disease in adulthood.

Clinical implication

This study adds new knowledge on the natural history of severe and moderate AAT deficiency. The results of good prognosis up to the age of 43–45 years may be useful when deciding the clinical follow-up of the PiZZ and PiSZ individuals. Liver disease in the deceased PiSZ subjects is a caution. Regular monitoring of liver function and the use of imaging techniques in PiZZ and PiSZ individuals may be of importance for early detection of liver disease. The American Thoracic Society/European Respiratory Society has recommended a regular assessment by liver function tests in PiZZ individuals.[1] However, it is unclear whether these liver function tests can be used to predict or identify liver disease. Prevention and identification of risk factors are crucial to stop the progression of liver disease.

Strengths

This cohort is the one of the most important existing, population-based, epidemiological study on the natural history of severe and moderate AAT deficiency that was started by a neonatal screening of all newborn infants in Sweden. Because each citizen living in Sweden has a unique identification number, the vital status was known for all subjects in the cohort. In comparison, the Oregon State Public Health Laboratory screened 107,038 newborn infants in 1971–1974 and identified 21 PiZ infants. These infants were followed-up in childhood, but after the age of 3–6 years, no reports have been published.[21]

Limitations

No control group from the general population has been followed up since birth. Therefore, the data are compared with the Swedish general population using the calculated SMR. Another limitation is that the low number of deceased subjects makes the statistical analysis of the difference in survival between the AAT-deficient individuals and the Swedish general population difficult.

Conclusion

PiZZ and PiSZ individuals have a similar life expectancy as the Swedish general population up to the age of 43–45 year of age. The majority of deaths occurred during childhood and were liver-associated mortalities.

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Disclosure

The authors report no conflicts of interest in this work.

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