Alpha-1 Antitrypsin Deficiency - Clinical Aspects and Management

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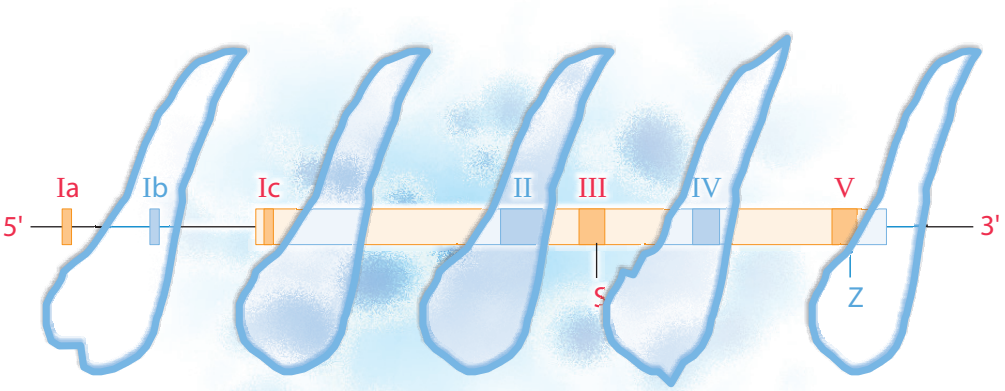

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Clinical Aspects and Management

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MEDICINE - STATE OF THE ART

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Preface

Alpha-1 antitrypsin deficiency is a common genetic disorder in Caucasians of European descent. Its first description was less than 50 years ago, but in this time, enormous efforts have been made to understand the genetic mechanisms, pathophysiology, and typical clinical manifestations.

In all populations with relevant prevalence of alpha-1 antitrypsin, it is still one of the most under-recognized diseases. Identification of patients, and establishing sufficient preventive and therapeutic measures necessitates at least a basic level of knowledge about alpha-1 antitrypsin deficiency among medical professionals. To improve awareness and to spread information, the first edition of this book was published in Germany in the year 2003.

The feedback from physicians, patients, and patients organisations was overwhelmingly positive. Colleagues from abroad encouraged us to translate our updated manuscripts into English, thereby making the content of the book accessible to a greater audience.

The authors intend to provide basic information about the most important aspects of alpha-1 antitrypsin deficiency in a short and comprehensive style. We hope that this book may serve as a valuable source of information for clinical aspects and management of patients.

Hannover, December 2006

Thomas Köhnlein
Tobias Welte

Foreword

Given the opportunity to write a foreword to the English version of the present volume I have chosen to recapitulate my personal experience of alpha-1 (PiZZ) at the University Hospital in Malmö, where the condition was first observed and defined. I chose to focus on the 35-year period from mid-1962 to mid-1997*. Although alpha-1 antitrypsin deficiency is a prevalent genetic disorder among Caucasians of European descent, it seems to be widely underdiagnosed. The reasons are several; the defect was described as late as 1963, the phenotypic expression is variable and an unknown proportion of subjects, probably about 30 % or more, can have a completely normal or even prolonged life span. Today, very limited information concerning final outcome is available. Most published studies are hospital-based and dominated by lung cases. Never-smokers are generally under-represented, resulting in an over-representation of fatalities caused by respiratory failure. In an attempt to improve knowledge of the natural history, we studied the cause-specific mortality in severe alpha-1 antitrypsin deficiency (only PiZZ) in a defined population of the city of Malmö, Sweden, characterized by both high detection and autopsy rates. This alpha-1 antitrypsin deficiency cohort represents an effort to trace all PiZZ-individuals in one defined population of close to a quarter of a million, ensure a long-term clinical follow-up, and if possible, a complete and standardized post-mortem examination. The expected number of PiZZ-individuals was estimated at 58 (96,600 citizens, who had died during the study period, divided by the PiZZ-prevalence in the population, 1/1700). Of the expected 58 cases, 41 (70 %) had been medically recognized. A postmortem examination had been performed in 37 (88 %). There was only one child, a boy dying from cirrhosis at age 4 months. Of the 40 adult individuals, there were 21 females and 19 men. Seventeen were never-smokers and 23 smokers (including ex-smokers). All relevant hospital records, autopsy protocols and death certificates were analyzed to determine the main cause of death. In addition, records were analyzed with respect to occurrence of diabetes, hypertension, myocardial infarction, and cerebrovascular disease. Mean age at death of adults was 64 years. As expected, smokers lives were shorter than that of never-smokers (56 vs. 73 years, $p < 0.01$). Respiratory failure ($n = 17$) due mostly to lower lobe, bullous and panacinar emphysema, was the main cause of death in this group. However, three never-smokers also died of the same cause (Figure 1).

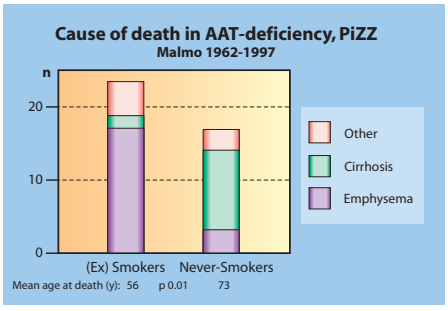

Figure 1: Cause of death in patients with alpha-1 antitrypsin (AAT) deficiency. The Malmö cohort 1962-1997.

The most impressive finding was the high incidence of cirrhosis among elderly never-smokers, 12 of 17 (70 %) vs. 2 of 23 (9 %) among smokers. Cirrhosis had been clinically diagnosed during life in the majority of these cases. Malignant transformation was seen in 5 of 14 cirrhotic cases. Alcohol was a contributing factor in only one individual. Hepatitis B- and C-markers were absent. Cirrhosis is predominantly a complication in the elderly, never-smoking alpha-1 antitrypsin-deficient individuals who have survived without development of severe premature emphysema. In rare cases (2-3 %), cirrhosis occurs prematurely in

*Presented in a preliminary form in proceedings of the first scientific meeting of the Alpha One International Registry (AIR) Como, 1999. Ed. M. Luisetti and R.A. Stockley, p. 15-20, Pavia, 2000.

individuals aged 20 or younger. It is evident that incidence of cirrhosis in alpha-1 antitrypsin deficiency has been underestimated. An association between alpha-1 antitrypsin deficiency and cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) positive vasculitis, as well as aneurysmal disease and necrotizing panniculitis, have been documented repeatedly.

Nephropathy was present in two individuals. In a female dying from hemorrhagic pneumonia glomerulopathy was diagnosed. In a cirrhotic male dying from complications of a bleeding duodenal ulcer, interstitial nephropathy and emphysema were observed. The causal relationship between alpha-1 antitrypsin deficiency and kidney disease in these two cases is uncertain and requires further study. The only case of hypertension was present in the male individual. There was also a strikingly low incidence of diabetes (one case), myocardial infarction, and stroke. Surprisingly, two cases of pancreatic islet-cell tumors, one benign insulinoma-like in a male dying from cirrhosis and severe encephalopathy, and one undifferentiated malignant endocrine tumor in a middle-aged woman, were observed. Considering the rarity of such tumors ($< 10^{-6}$), the incidence of these tumors in two out of 40 alpha-1 antitrypsin deficiency cases is probably related to islet-cell hyperplasia, a universal and unexplained feature of alpha-1 antitrypsin deficiency. An accumulation of polymerized Z-alpha-1 antitrypsin was observed in the islet cells, where it may influence the sequential development of hyperplastic islets to benign and malignant tumors.

Taken together, these observations led to the simple assumption that islet-cell hyperplasia in alpha-1 antitrypsin deficiency, whatever its cause, might have a functional role, ie, to preserve insulin secretion to confer a metabolic advantage by influencing incidence of diabetes. To study the putative effect of alpha-1 antitrypsin deficiency on the lifetime incidence of diabetes and its atherosclerotic complications, investigators took advantage of the high autopsy frequency in the population. A retrospective case-control study based on autopsied alpha-1 antitrypsin-deficient patients was therefore conducted. Each eligible autopsied PiZZ case (n = 32) was matched (sex and age) with four controls (n = 128) from the same autopsy register, and the Mantel-Haenszel odds ratio (OR_{mh}) was calculated. The results indicated a strong negative correlation between alpha-1 antitrypsin deficiency and life-time incidence of diabetes (OR = 0.24), hypertension (OR = 0.21), myocardial infarction (OR = 0.21), and stroke (OR = 0.18) compatible with a possible survival advantage in alpha-1 antitrypsin deficiency.

In the future, the disease spectrum of alpha-1 antitrypsin deficiency may change considerably as a consequence of changing smoking habits. The predominance of alpha-1 antitrypsin deficiency–related emphysema in populations of European descent, which have the highest Z-gene frequencies, will hopefully gradually decrease. In contrast, the incidence of neonatal cholestasis and cirrhosis in the young and in the elderly never-smoker will remain unaffected. In the future the latter group will probably dominate the disease spectrum.

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