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Mortality in hereditary antithrombin-III deficiency—1830 to 1989

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To determine whether antithrombin-III (AT-III) deficiency leads to an excess mortality, we studied 171 individuals from ten families with a proven hereditary deficiency. 73 were classified as certainly deficient either by direct measurement of AT-III concentration or by mendelian inheritance patterns. 98 individuals had a high probability (0·5) of deficiency. The 64 deaths recorded did not exceed those expected for the general population adjusted for age, sex, and calendar period. We suggest that a policy of prophylactic anticoagulation for patients with AT-III deficiency cannot be recommended.

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Introduction

Hereditary antithrombin-III (AT-III) deficiency is an uncommon autosomal disorder that is associated with a tendency to venous thromboembolism in heterozygous individuals.[1,2] The severity of venous thrombosis ranges from superficial thrombophlebitis to pulmonary embolism but the risk of severe thromboembolism in AT-III deficient individuals is largely unknown.

The decision to anticoagulate symptom-free AT-III deficient individuals prophylactically is therefore difficult and a randomised trial of anticoagulant treatment against placebo is unfeasible since the disorder is rare and a long

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follow-up would be required to give a definitive answer. Furthermore, the risks of long-term anticoagulant treatment are substantial.[3]

To study the natural history of AT-III deficiency, we compared mortality in AT-III deficient families with that of the general population. If the mortality were lower in the general population, one could estimate the potentially beneficial effect of anticoagulant treatment.

Subjects and methods

Study population

All Dutch families, with a member known to be AT-III deficient and who was under the care of the Departments of Haematology of the University Hospitals of either Leiden or Amsterdam, were eligible for study. Diagnosis was based on AT-III antigen concentrations less than 75% of normal, in the absence of heparin treatment, chronic liver disease, or nephrotic syndrome. Only families with 2 or more deficient individuals were studied, to avoid inclusion of patients with an acquired deficiency. Furthermore, we included only families with at least one symptomatic deficient individual.

In all families, non-deficient individuals were excluded and for untested family members information from relatives was used to assign a probability of deficiency. Since AT-III deficiency is an autosomal disorder, some untested individuals can be taken as heterozygous for AT-III deficiency—these family members have passed on the affected gene from common ancestors to deficient individuals. Mendelian probabilities can be assigned to all individuals in a pedigree. We restricted our study population to those who were deficient with certainty or had a probability of deficiency of 0·5. We rejected the possibility of recent mutations, which may theoretically have taken place in smaller pedigrees, because of the low frequency of AT-III deficiency. This method requires complete pedigrees. Since 1809 it has been mandatory by law in the Netherlands to report all births and deaths to the municipal registries. All information in this study has been verified by reference to these municipal and national registries.

Analysis

The mortality of the study population (observed) was compared with the general population adjusted for age, sex, and calendar period (expected). The ratio of observed to expected number of deaths (O/E) is the standardised mortality ratio (SMR). The expected mortality is derived by multiplying the total number of years lived by the study population in each calendar period, and for each age and sex category, by the mortality rates (age and sex specific) of the general population for each calendar period. Confidence limits for the SMR are based on a Poisson distribution for the observed number of deaths.[4]

Calendar periods were divided into twenty-year intervals from 1830 to 1989, and to each of these we applied the population mortality rates of the mid-interval year, from 1840 onwards. In each calendar period we subdivided by sex and age class (0–1 yr, 1–4 yrs, 5–9 yrs, and beyond in five-year age groups). Population mortality rates were obtained from the Central Bureau of Statistics. To eliminate bias that may have led to a spuriously low SMR, we ignored the first two decades of life, both for observed and expected mortality, the explanation being that those who passed on the gene to their descendents had to live until reproductive age before they could do so. This reason did not apply for those assigned a 0·5 probability of deficiency. In addition, we analysed mortality by age.

Results

We identified ten families with 2 or more AT-III-deficient individuals and at least one symptomatic deficient individual. The cutoff concentration for AT-III antigen of 75% of normal was satisfactory because all measurements were either less than 69% (taken as deficient) or greater than 83% (normal). 73 classified as deficient with certainty: 23 based on information on family members (in 16 confirmed by AT-III measurement) and 50 based on low AT-III plasma concentrations. In addition, 98 individuals had a 0·5 probability of deficiency. No subject was lost to follow-up. The smallest family contributed 6 subjects to the study group, and the largest, 39. Three to six generations were represented in these families. Birth year and year of death ranged from 1830 to 1989 and 1899 to 1987, respectively.

Of a total of 8168 person-years (all ages combined), 64 deaths took place. There were 5066 person-years in the over 20 age group and 56 deaths. 65% of those who died were born before 1900, while 55% died before 1950. Mean age of death was 57 years, median 66 yr). The mortality in the study group did not differ from that of the general population. The expected number of deaths was 58·8 (aged 20 years and older). The relative mortality was 1·0 (O/E, 56/58·8; SMR, 1·0; 95% confidence interval, 0·7–1·2). In the group classified as deficient with certainty there was no excess mortality: 9 deaths took place compared with 9·8 deaths expected (SMR, 0·9; 95% CI, 0·4–1·6). Subjects with a 0·5 probability of deficiency also had a mortality frequency comparable with the general population (O/E, 47/48·9; SMR, 1·0; 95% CI, 0·7–1·3). For men > 20 yrs, the SMR was 0·9 (O/E, 36/41·9; 95% CI, 0·6–1·2), and in women the SMR was 1·2 (O/E, 20/16·9; 95% CI, 0·7–1·8). In addition, although a deficiency of AT-III may increase risk of postpartum thrombosis, there was no excess

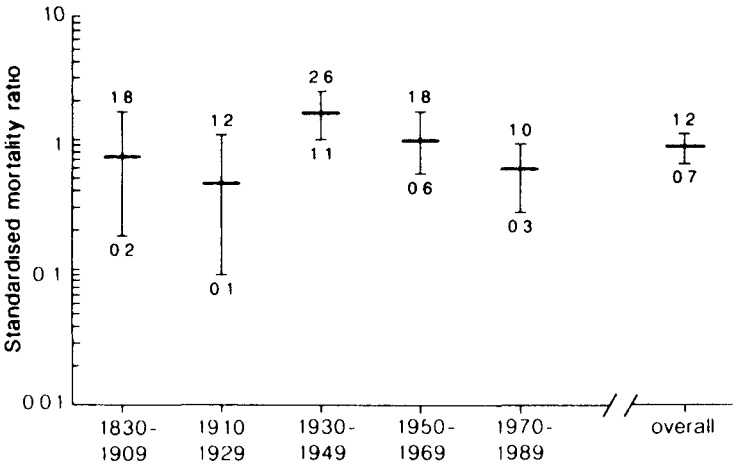

Fig 1—Mortality in AT-III deficiency by calendar period

mortality in women aged 20–40 yrs (O/E, 3/2·5; SMR, 1·2; 95% CI, 0·2–3·0).

Figure 1 shows the relative mortality for different calendar periods from 1830 to the present. Although some variation exists, AT-III deficiency does not appear to lead to excess mortality. Figure 2 shows the mortality ratio for different age groups and includes those subjects aged ≤ 19. In this young group, relative mortality is low (O/E, 8/27·5; SMR, 0·3). This may be because of preferential inclusion of those who had children or under-reporting of child deaths in the nineteenth century. In all other age groups observed mortality was equal to expected mortality.

Discussion

We studied the natural history and mortality of AT-III deficiency since most individuals in our study group lived before anticoagulant therapy became available. No excess mortality was found and confidence intervals were narrow. In any genetic study there is a risk of bias and although the frequency of AT-III deficiency in the general population is low, the recruitment of affected family members was probably incomplete because not every individual will manifest venous thromboembolism. Incomplete data collection will lead to a biased estimate only if AT-III deficiency runs a different course in different families and breeds true within those families. Severely affected families are then more likely to be included than mildly affected families and so mortality may be overestimated. Since no excess mortality was found, this possibility is unlikely. Part of the study group only had a probability of being deficient

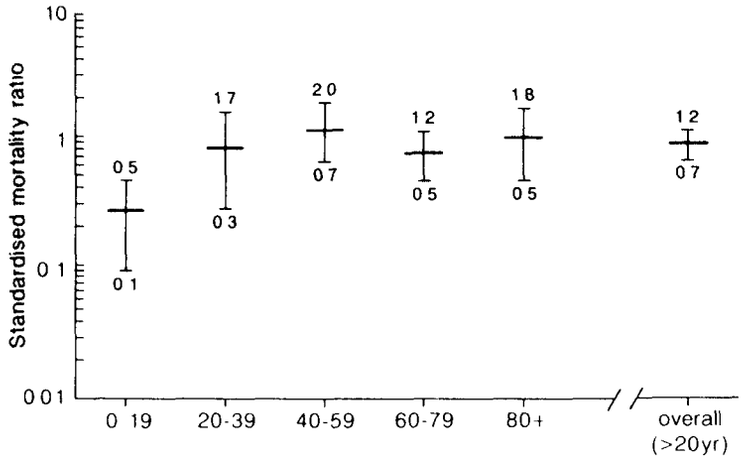

Fig 2—Mortality in AT-III deficiency by age

in AT-III and therefore some individuals may, in reality, have had normal AT-III concentrations. However, we found no excess mortality in the subgroup of individuals proven to be deficient. The inclusion of individuals with a 0·5 probability of deficiency allowed us to both increase the statistical power of the analysis by extending the study back to 1830 and reduce bias by selecting those who reproduced or were tested.

Life-long anticoagulant treatment is probably indicated after a first episode of thromboembolism.[5,6] The need for long-term prophylaxis with anticoagulants in symptom-free AT-III deficient individuals is uncertain.[7] Some groups recommend life-long prophylaxis in all deficient individuals,[5] while others argue that anticoagulation should be reserved for those with additional risk factors for or a previous history of thromboembolism.[6-8] Until now, evidence has been confined to case reports. Our study, in complete family pedigrees, suggests that life-long treatment with anticoagulants in symptom-free AT-III deficient individuals is unlikely to improve survival.

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