British Journal of Haematology, 1994, 87, 348–352

The family history and inherited thrombophilia

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Received 20 December 1993; accepted for publication 7 February 1994

Summary. The role of the family history as a tool for the diagnosis of inherited thrombophilia has not been established. Several authors have indicated that a positive family history is not a good predictor of inherited abnormalities such as antithrombin III deficiency, or deficiencies of protein C or protein S. We have tried to approach the family history in a quantitative way. To this end we used the cumulative incidence data of thrombosis in the general population and also in a population of protein C deficient families to estimate the expected number of symptomatic subjects in a family under both the hypothesis of inherited thrombophilia and the null-hypothesis. Although a number of assumptions underlying our calculations need to be verified and probably adjusted before any truly quantitative meaning can be assigned to this approach, we feel that the family history is a useful diagnostic test for inherited thrombophilia if it is used in a critical way.

Keywords: thrombophilia, family history, venous thrombosis.

Inherited venous thrombophilia has been an area of intense clinical research since the description of the deficiency of antithrombin III (Egeberg, 1965), protein C (Griffin *et al*, 1981; Bertina *et al*, 1982; Broekmans *et al*, 1983) and protein S (Comp *et al*, 1984; Broekmans *et al*, 1985). The family history is considered as an important tool for the distinction between sporadic and familial cases of venous thrombo-embolic disease. This distinction is important for two reasons. Firstly, the suspicion of an inherited tendency to thrombosis justifies the request of fairly extensive laboratory tests for individual patients. Secondly, the search for 'new causes' of inherited thrombophilia requires a panel of families with idiopathic familial thrombophilia. New tests can then be applied in such families. Using this approach we analysed the genes for thrombomodulin and tissue factor pathway inhibitor in the index cases of 30 families with unexplained familial venous thrombophilia without finding any abnormality (P. H. Reitsma *et al*, unpublished observations). For this approach to be successful, however, we need a criterion to decide whether the thrombosis in a family is likely to be associated with an inherited trait.

The purpose of this study was to quantitate the likelihood that thrombosis in a particular family is associated with an inherited abnormality, even if that abnormality defies laboratory identification.

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MATERIALS AND METHODS

Cumulative thrombosis incidence in the general population. The catchment area of the Leiden regional anticoagulation clinic comprises about 500 000 inhabitants. Any patient requiring treatment with oral anticoagulants within this area is referred to the anticoagulation clinic for monitoring of the intensity of the treatment. For each patient the indications for the treatment are registered in a computer database; also personal data, accompanying illnesses, all prothrombin times, dosages, and complications.

To calculate the numerators for age-specific thrombosis incidence rates we extracted all subjects from the computer files who were treated for a first episode of deep vein thrombosis or pulmonary embolism during 1986 and their age at the time of diagnosis. Unfortunately, the use of objective diagnosis for deep vein thrombosis was (and still is) not used in all cases. The denominators were obtained using the population data from the municipal registries of the same catchment area. The number of new cases of deep vein thrombosis of pulmonary embolism within each 5-year age interval were divided by the total number of thrombosis-free patient-years in the Leiden area within that age class, over the 1 year period of follow-up. Subsequently, cumulative incidences, i.e. the probabilities of having had a first thrombotic episode before a given age, were calculated

from equation 1 (Rothman, 1986):

$$CI = 1 - e^{-\Sigma(t \times IR)} \quad (1)$$

where CI = cumulative incidence, e = base of the natural logarithm, t = width of the time intervals (5 years) and IR = age-specific incidence rates. Finally, a graph was made by plotting the cumulative incidences against age.

Cumulative thrombosis incidence in protein C deficiency. A cumulative incidence of first episodes of deep vein thrombosis or pulmonary embolism in protein C deficiency was obtained from data on 75 subjects with a DNA-based diagnosis of protein C deficiency from 20 different families (Allaart *et al*, 1993). In order to avoid bias, all index cases from these families were excluded.

Expected number of symptomatic subjects within a family. Using the cumulative incidence plots we can predict the probability to have had at least one episode of deep vein thrombosis or pulmonary embolism for any person of a particular age in a pedigree. This probability can be calculated under the hypothesis that the family is not affected by an inherited risk factor for thrombophilia by using the cumulative incidence graph for the population and the age of the subject. On the other hand, in order to calculate the probability under the hypothesis that the family is affected by protein C deficiency or a risk factor of similar strength, we use both the cumulative incidence plot for the population and the plot for the protein C deficient subjects. In this case, the probability to have had at least one thrombotic episode is given by the following equation:

$$P_{sympt} = P_{non\text{-}def} \times CI_{non\text{-}def} + P_{def} \times CI_{def} \quad (2)$$

where P_{sympt} = the probability to have suffered one or more episodes of deep vein thrombosis or pulmonary embolism at the relevant age, $P_{non\text{-}def}$ = the probability not to have inherited the deficiency based on the assumption that the index case is deficient and the deficiency is transmitted in an autosomal dominant fashion, $CI_{non\text{-}def}$ = the cumulative incidence of deep vein thrombosis or pulmonary embolism at the relevant age for subjects in the population at large, P_{def} = the probability to have inherited the deficiency based on the assumption that the index case is deficient and the deficiency is transmitted in an autosomal dominant fashion ($P_{def} = 1 - P_{non\text{-}def}$), CI_{def} = the cumulative incidence of deep vein thrombosis or pulmonary embolism at the relevant age for subjects with protein C deficiency. The expected total number of symptomatic relatives is obtained by adding up the individual probabilities for all the subjects in the pedigree of the index case.

The probability that the index case has an inherited risk factor. This calculation requires three sources of information, which are combined using Bayes' theorem:

1. Information on the family 'anterior to' the index case, i.e. the number of symptomatic relatives observed in relation to the number of symptomatic relatives as expected under both hypotheses; for the sake of simplicity we have not taken into account information about the descendents ('posterior to') of the index case,

2. Information about the index case, i.e. the age at which he suffered his first DVT,

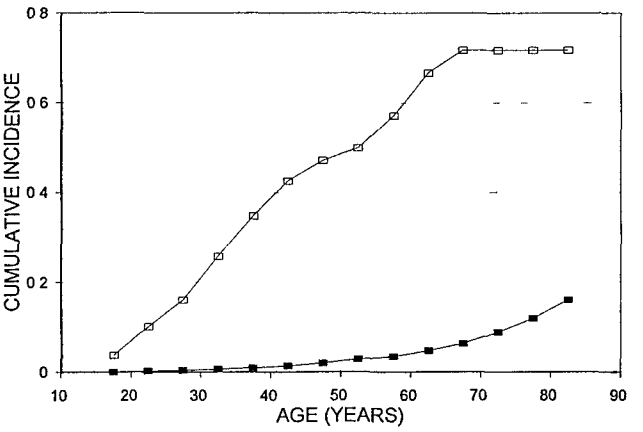

Fig 1. The cumulative incidence of thrombosis in patients with definite protein C deficiency (□) and in the general population (■).

3. The prevalence of the hereditary traits.

Ad 1. To calculate the ratio of the likelihood favouring inherited thrombophilia of the family (LR_{family}) under the hypothesis that the index case has an inherited risk factor and the likelihood of the family under the hypothesis that the index case does not have an inherited risk factor, it is assumed that the number of symptomatic relatives under both hypotheses follows a Poisson distribution. This means that under both hypotheses the means and the variances are equal. In practice this assumption is reasonable, although the variance will be a little smaller than the corresponding mean. The calculation is given in equation 3 (Sackett *et al*, 1985):

$$LR_{family} = \exp\left[obs \times \ln\left(\frac{\mu_{inherited}}{\mu_{chance}}\right) - (\mu_{inherited} - \mu_{chance})\right] \quad (3)$$

where obs = number of relatives observed to be symptomatic, $\mu_{inherited}$ = the expected number of symptomatic relatives under the hypothesis of inherited thrombophilia, and μ_{chance} = the expected number of symptomatic relatives under the null-hypothesis.

Ad 2. From Fig 1 we can predict that the index case at age 48 has a 47% probability to have suffered a venous thromboembolic event under the thrombophilia hypothesis and a 2% probability under the null-hypothesis. This implies a likelihood ratio (LR_{index}) favouring thrombophilia of 47/2. Although it would be better to use the age-specific incidence at age 48 instead of the cumulative incidence up to age 48, our approach allows for easy application of the two curves and is a reasonable estimate.

Ad 3. We assume a prevalence (p_0) of inherited thrombophilia traits of slightly over 5% in the population (Miletich *et al*, 1987; Tait *et al*, 1993; Koster *et al*, 1993). The final probability P_{final} for the index case to have inherited a thrombophilia gene is calculated by multiplying the two likelihood ratios and by subsequently using Bayes' theorem (Bayes, 1763) to combine the prevalence p_0 with the combined likelihood ratio ($LR_{combined}$) as shown in

Table I. Age-specific incidence rates and cumulative incidences of thrombosis in the population of the Leiden regional anticoagulation clinic.

Age (years)	Population* (No.)	No. of cases	Incidence rate (per 1000 per year)	Cumulative incidence†
0–4	26259	0	0·00	0·000
5–9	26900	0	0·00	0·000
10–14	28044	1	0·04	0·000
15–19	34874	4	0·11	0·001
20–24	38335	19	0·50	0·003
25–29	35497	8	0·23	0·004
30–34	30977	15	0·48	0·007
35–39	32496	20	0·62	0·010
40–44	27319	25	0·92	0·014
45–49	21581	25	1·16	0·020
50–54	18599	35	1·88	0·029
55–59	16478	23	1·40	0·036
60–64	14394	39	2·71	0·049
65–69	11841	42	3·55	0·066
70–74	9986	58	5·81	0·092
75–79	7504	58	7·73	0·127
80–	7688	82	10·67	0·172

*Thrombosis-free population was calculated by correcting the population number for the cumulative incidence in the previous age category.

† See Methods.

equations 4 and 5:

$$LR_{family} \times LR_{index} = LR_{combined} \quad (4)$$

$$P_{final} = \frac{LR_{combined} \times p_0}{LR_{combined} \times p_0 + 1 - p_0} \quad (5)$$

RESULTS

The population-based age-specific incidence rates for deep vein thrombosis and pulmonary embolism in the catchment area of the Leiden anticoagulation clinic, and also the cumulative incidences for each of the age intervals, are presented in Table I. Based on these data and the data from Allaart *et al* (1993), a graph was made of cumulative

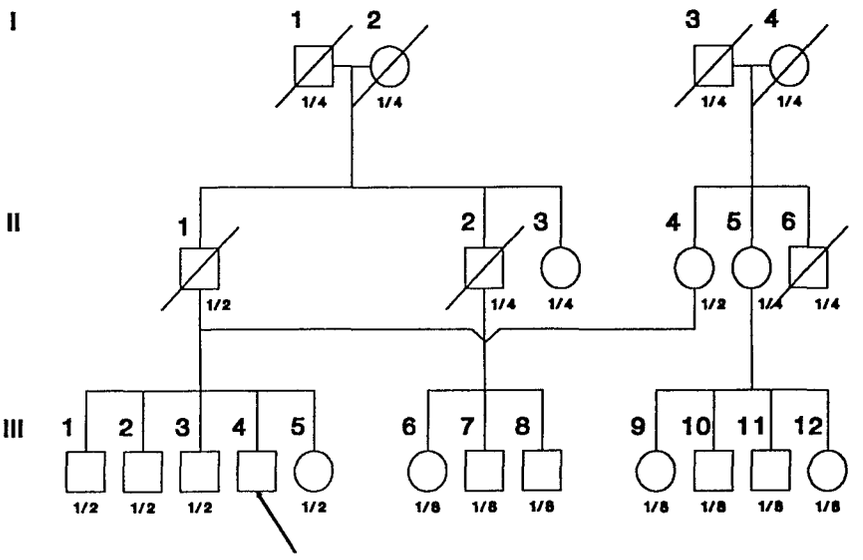

Fig 2. The pedigree of an imaginary index case (III.4). Assuming that the index case has an autosomal dominant inherited thrombophilia trait we calculated the probabilities for the relatives to have the same abnormality; the probability is indicated below each subject. Men are indicated by □, women by ○, deceased subjects by an oblique line, and the index case by an arrow.

Table II. Life-time thrombosis risk for the relatives of the index case, calculated for the null hypothesis as well as the thrombophilia hypothesis.

		Risk to have had DVT or PE	
Subject	Age*	Null hypothesis	Thrombophilia hypothesis
I.1	83	0·172	0·717
I.2	62	0·049	0·666
I.3	80	0·172	0·717
I.4	86	0·172	0·717
II.1	72	0·092	0·717
II.2	77	0·127	0·717
II.3	78	0·127	0·717
II.4	82	0·172	0·717
II.5	80	0·172	0·717
II.6	25	0·004	0·161
III.1	54	0·029	0·500
III.2	52	0·029	0·500
III.3	50	0·029	0·500
III.4	48	Index case	Index case
III.5	44	0·014	0·427
III.6	48	0·020	0·473
III.7	46	0·020	0·473
III.8	42	0·014	0·427
III.9	54	0·029	0·500
III.10	52	0·029	0·500
III.11	49	0·020	0·473
III.12	47	0·020	0·473

* At death or current.

incidence versus age, both for the population-based data and for the subjects with protein C deficiency (Fig 1).

In order to illustrate the use of these data for the prediction of the number of symptomatic subjects within the family of an index case, we present the pedigree of an imaginary patient with deep vein thrombosis (III.4) in Fig 2. Using the age of the relatives and the population-based plot of Fig 1, we first calculated the risk to have had deep vein thrombosis or pulmonary embolism for each relative under the hypothesis that the family is not affected by an inherited risk factor for venous thrombosis. The expected number of affected relatives adds up to 1·5 (Table II).

In order to calculate the risk to have had thrombosis under the thrombophilia hypothesis, we first applied Mendelian reasoning to assign a risk for carriership of the thrombophilia trait for each relative. To this end we assume that the index case is affected with this trait and that the trait is inherited in an autosomal dominant fashion. Both parents (II.1 and II.4) were assigned a risk of 1/2 and the four grandparents (I.1 to I.4) a risk of 1/4. Subsequently, brothers and sisters (III.1, III.2, III.3, III.5) were assigned a risk of 1/2, aunts and uncles (II.2, II.3, II.5, II.6) a risk of 1/4 and cousins and nieces (III.6 to III.12) a risk of 1/8. Next, the probability to have had thrombosis was calculated for all family members using equation 2. Under the thrombophilia hypothesis, the expecteed number of symptomatic relatives adds up to 4·3.

Table III. Final probability of inherited thrombophilia for the index case in the family shown in Fig 2, based on the data of Table II, the assumption that the prevalence of inherited thrombophilia genes is 5% in the population, and the assumption that the occurrence of thrombotic events follows a Poisson distribution.*

No. of symptomatic relatives	LR_{family}	LR_{index} DVT at age 48	Final probability
Unknown	1	47/2	0·55
0	0·06	47/2	0·07
1	0·17	47/2	0·17
2	0·50	47/2	0·38
3	1·4	47/2	0·63
4	4·1	47/2	0·84
5	11·8	47/2	0·94

* See Methods for explanation.

From Fig 1 we also obtained the likelihood ratio favouring thrombophilia for the index case. At the age of the index case (48 years) this ratio amounted to 47/2. Subsequently, by combining the two likelihood ratios and the prevalence, the final probability of inherited thrombophilia in the index case was calculated for varying numbers of symptomatic relatives. The results of this calculation are shown in Table III and clearly indicate the important contribution of the family history.

DISCUSSION

This study demonstrates that a family history for venous thrombosis or embolism cannot be interpreted without considering the number of relatives and their ages. The commonly applied criterion of a single symptomatic relative for the family history to 'positive' (Engesser *et al*, 1987; Heijboer *et al*, 1990) is not sufficiently strict for all but the shortest pedigrees. When we carried out a national thrombophilia survey in The Netherlands we found a satisfactory explanation for thrombophilia in only one out of three families with a positive family history (Briet *et al*, 1987); Heijboer *et al* (1990) found an even lower figure. We explained this finding by the existence of unknown causes of thrombophilia, which was recently shown to be true by the finding of Dahlbäck *et al* (1993) and subsequently by ourselves (Koster *et al*, 1993) that many cases of idiopathic thrombophilia are due to a resistance against activated protein C. However, a low cut-off point for the family history to be considered positive is bound to produce a low predictive value for the family history.

The calculation of likelihood ratios favouring a thrombophilia trait as presented here is obviously a simplification. It is clear that some cases with thrombosis are more likely to be associated with thrombophilia than others. A young man with spontaneous mesenteric vein thrombosis is more likely to suffer from antithrombin III deficiency than an 80-year-old who has deep venous thrombosis after total hip

replacement. The results shown in Table III do not accomodate such information. Similarly, we have assumed that all inherited risk factors carry risks of the same magnitude. For protein C and the resistance to activated protein C this assumption is probably correct (Allaart *et al*, 1993; Koster *et al*, 1993). Whether this is also true for antithrombin III and protein S remains to be determined, but it is unlikely that this affects our discussion in a significant way. Furthermore, we have not taken into account the somewhat higher thrombosis risk of women. Finally, if objective diagnosis could be applied in all cases, the incidence of thrombosis in the population at large as well as in the protein C deficiency group would decrease. Consequently, the overall effect on the outcome of our calculations is probably not important. Further work is necessary to take these considerations into account.

It will be difficult for all thrombosis centres to collect reference data on the population at large, and even more difficult to collect them on families with protein C deficiency or other thrombophilias. Regional differences in the incidence of thrombosis in either group depend more on the ascertainment of the diagnosis than on true variations in the thrombosis incidence. For this reason we do not think that it is necessary to collect local data in order to apply our approach to the family history. Another factor that is difficult to take into account is the reliability of the family history; the only solution for this is to persevere and to get professional confirmation of any information about thrombotic events.

The importance of our quantitative approach is two-fold. First, the search for the causes of hitherto idiopathic familial thrombophilia must be based on families with an excessive number of patients with thrombosis, or the efforts will be fruitless. Second, unnecessary diagnostic tests in individual patients can be avoided if the history is used in a critical way. Although the absolute figures in our example may be rough approximations, we find it safe to conclude that a single symptomatic relative is not sufficient evidence for the presence of inherited thrombophilia in an index case with deep vein thrombosis or pulmonary embolism.

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